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Seminar on Ballistocardiography

Foreword

IN THIS issue of the JOURNAL there appears the initial section of the Seminar on Ballistocardiography. We will include several chapters in each of the succeeding issues of the JOURNAL until the series is completed.

Many physicians who have attempted to follow the current literature on ballistocardiography have been overwhelmed by the quantity of material presented. Many abandoned any attempt to keep up with this flood and have been content to wait until such time as the ideas of the leaders in the field have crystallized. Because we believe that such a time has arrived, we have undertaken to prepare this Seminar for you.

This series aims to present a broad over-all view of the current status of the science so that the uninitiated reader can in a short time catch up with the most advanced thinking in the field. Abstract mathematical concepts have, for the most part, been avoided. The occasional exceptions were necessary because new areas now being explored could not be presented without first establishing mathematical background. The reader who is not mathematically inclined may omit these sections without losing the essence of the Seminar.

The entire Seminar represents a most ambitious survey of ballistocardiography. Every aspect of the subject is reviewed, usually by an authority who has done intensive and original work in that area. Every effort has been made to include protagonists of each and all of the divergent schools in the field.

Many of the contributors have stated specific preferences for one instrument over another or one method over another, not an altogether unusual situation to find existing among widespread laboratories. Many of the contributors still maintain a healthy conservatism toward the conclusions that can be drawn from this or that specific clinical application. This too is quite reasonable. Although ballistocardiography is less empiric a branch than is electrocardiography, it is still very young and deals with many unknowns; it must proceed slowly and cautiously.

Yet, with all of this, the number of instances where the findings or opinions expressed are in conflict is small, and even these differences relate to the research rather than the clinical application of the BCG method. It appears that the clinical (as opposed to the research laboratory) interpretation of the ballistocardiogram requires only that a good tracing be differentiated from a poor tracing. This is achieved by any accurate ballistocardiogram. On the other hand, the interpretation of the borderline ballistocardiograms, of minor deviations on those tracings that are neither good nor bad, is still a research problem requiring the most precise and advanced methodology. To reject the clinical use of the ballistocardiogram on this account is equivalent to rejecting the clinical 12 lead elec-

trocardiogram because there is more information present in the three dimension spatial loop vectorcardiogram.

Practicing physicians are conservative by inclination, training, and experience. This is altogether proper. The old dictum, "Be not the first to try the new, etc." is still very good over-all advice for those who are most directly concerned with the care of the patient. The lack of unanimity (to state it very conservatively) among those who were developing the ballistocardiographic method did not tend to dispel the fears of those who were viewing with askance the lusty, howling ballistocardiograph infant. Nevertheless, we believed from the onset that there were large areas of agreement among all the protagonists and that the differences between them were more apparent than real. And so it seems to have worked out. Although many divergent views are presented in the papers that follow, all are agreed that the ballistocardiogram gives clinically important information right now. We invite you to read on, absorb some of our enthusiasm, and join us in ballistocardiography.

We wish to extend sincere thanks to our distinguished contributors. Their enthusiastic cooperation and support has made this Seminar possible.

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Introduction

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WHEN a patient suffers from weakness of an arm or leg, all doctors test the strength of the muscle's contraction and note the coordination, or incoordination, of the movement. Such tests are useful not only to determine the original degree of abnormality but also to try the effect of therapy upon it. The anatomic lesions, which may or may not accompany these abnormalities of function, receive far less attention than the demonstration of the abnormalities themselves.

That the heart muscle, like the peripheral muscles, suffers from diseases which sap its strength would be conceded by everyone, but because it is not so readily available to direct testing, the problem of evaluating cardiac strength or weakness, coordination or incoordination, has been much more difficult. In the distant past skillful palpation of the pulse was relied upon to give information about cardiac strength. But later, perhaps in reaction to extravagant and fanciful interpretations of the significance of the pulse, interest declined. Indeed we have passed through an era when most doctors paid little attention to estimations of cardiac strength or weakness although the concept continued to play an important part in their thoughts about heart disease. In recent years, if an opinion on the heart's strength or weakness was written into the records at all, it was usually based on evidence of a most uncertain kind, such as the loudness of the heart sounds and the height of venous pressure. Clinical interest has been concentrated on the electrocardiogram, a record of great interest but one altogether unrelated to cardiac strength or weakness, and on information which would permit one to identify the nature and position of the heart's anatomic lesions. This attitude is in sharp contrast to that of our profession with regard to diseases involving peripheral muscles.

This is not said in criticism; the recent advances in the surgery of the heart were made possible by those who developed the means of anatomic diagnosis. But the heart is a pump, and profound changes in its contracting power may occur without any anatomic changes now known. This was born in on me when, working in Professor Richards' laboratory of Pharmacology, we conducted animal experiments and watched the heart, subjected to the full action of certain drugs, beat more and more feebly until it stopped altogether. Or, subject to poisonous doses of other drugs, the heart would lose the fine coordination of the normal contraction, the movement of the various parts losing their proper relation to one another until the units contracted independently and the ability to pump the blood was lost. But when the heart was then examined no anatomic lesions were to be found.

Certainly similar abnormalities of myocardial function are to be expected in disease. Indeed, information at hand suggests that such physiological heart failure is the common situation, demonstrated by the pathologist every day. For the heart always fails, at death, before necropsy is made, and anatomic lesions which might account for the failure to continue beating are found only in a small minority of cases. And most of the well-known lesions, present a long time, are certainly not the immediate cause of the terminal failure.

So it seems self-evident that knowledge of the strength or weakness of the heart's contraction and its internal coordination are of fundamental

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importance both for the detection of myocardial abnormality and to guide our therapeutic attack upon it, and that every effort should be made to devise and improve methods for securing this information.

The ballistocardiogram provides one such method, and that this record bears a close relation to the strength of the heart's contraction is the conclusion of everyone who has studied the problem. The method has certainly attracted wide interest; examination of the Index of the Armed Forces Medical Library shows that papers on the ballistocardiogram are appearing in the world's literature about once every three days. Monographs on the subject have recently been written in German, French (2), Italian, Spanish (2), Dutch, and Portugese. The first three clinical monographs, published in English several years ago, are now out of date.

This Seminar is designed to bring together the most recent information about the ballistocardiogram: its methods of application, sources of error, the interpretations now being made from such records, and the various opinions concerning their interest and general usefulness. Indeed this Seminar might well be said to celebrate the twenty-first birthday of the first instrument to bear the name of ballistocardiograph, with which clinical investigations were commenced in 1937, and at the same time to testify that, after the usual growing pains and difficulties of adolescence, the method may now be said to have come of age. The degree of success attained the reader can judge for himself.

Biophysical Aspects of Ballistocardiography*

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INTRODUCTION

A CARDIOLOGIST is interested in many aspects of ballistocardiography beyond the physical. The present development of this clinical art and science is however still limited seriously enough by physical problems, to start our discussion with this aspect. Rather than review again the history and literature,[9] we will try to interpret in less technical terms where the biophysical considerations now stand. In fine print we will put more specialized points for those more conversant with this field.

The ballistocardiogram (BCG) may be defined[1] as a record of body motions which result from cardiovascular action. This motion refers to the whole body, or thorax at least, rather than local kinetograms (as from chest, sides, shoulders, abdomen, hips, etc.):

The head-foot motion is sensed fairly well from the shins or head, but the A-P and lateral BCG requires some supporting device like a plate, bed, or chair, to average the complex movements of the individual body surfaces. The nature of this support will be seen to raise major problems; yet without such supports, reproducible or comparable records are difficult to get.

Specifically, the *motions* in question are the displacement (D), velocity (V) or acceleration (A) of the body, depending on what dynamic aspect of the cardiovascular driving action is desired. Since these drives on the body act at varying angles to its axis, they are vectorial and require sensing in three directions, just as with the ECG. One axis or "lead" of the BCG, the head-foot, is probably more informative than is a single lead of the ECG, but both the frontal (HF and RL) records are important and have been used routinely. However, the lateral BCG turns out far more difficult to record properly than the others.

Unlike the electrical case, mechanical forces ("voltages") on a body do not produce velocities ("currents") only, but also another kind of response: angular or rotational motion. Although in principle the rotational BCG vector can be specified *independently* of the translational BCG, in practice these are so coupled that one cannot simply neglect the rotation. In some cases the latter is overpowering, as we will show.

In addition to the *cardiovascular* forces, *external* forces as well operate on the body, strongly affecting the BCG. We now know that if the ground prevents free motion of the body or its support in any direction (whether translation or rotation), the BCG record becomes falsified by resonance artefacts. With the ECG, ground contact is easily avoided; with the BCG this still presents a major problem.

In addition, there are extra *internal* forces besides those of cardiovascular origin: the motional interaction forces of body segments and components, muscle action and respiratory displacements, which mix into or distort the effect of cardiovascular forces. These feed into the nonrigid mechanical network which transmits forces from blood via body to BCG sensing device, and so form a real part of the BCG record.

All this raises (to a biophysicist) the question of information. Is every detail on a BCG potentially useful information? For example, for clinical purposes, the neat periodic regularity of the usual "normal" direct-body record is not information; it tells mainly that the dorsal tissues are passively vibrating because they are touching "earth." However, a breakup of this regular pattern correlates with disease, and so

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becomes information. Information can be increased quantitatively by recording 9 traces: D, V, and A in HF (y), RL (x), and AP (z) directions of translation, plus 9 more for rotation, plus suitable physiology. This is polygraphy to the point of absurdity. It appears that neither physicians nor physicists alone can decide between artefact and information, relevant and irrelevant; but that for progress in this complex field, they supplement each other.

Before launching into details, we should take a perspective view of methodology. This is not only a matter of devising proper recording devices and suspensions. It is also deciding what questions to pose the cardiovascular system, to get the most information from it. What is the effect of posture? How much and in what way should cardiovascular stress be applied? How fast and by what physiologic route does it recover? The early BCG work[2] in fact was designed primarily to study cardiovascular stress. Does the current passive methodology perhaps neglect the dynamic or rate-information the BCG could give?

The objectives of ballistocardiography have shifted, according to the results realized from the methodology in vogue. Though *stroke-volume* measurement[3] was fairly successful with normals, with abnormals at rest it proved poor with the BCG methods then in use. Again the measurement of ejection *force* proved not to relate in a simple way to the resonant kind of records then current. The objectives at present focus more on details of the wave pattern: as related to valves, blood pressure, age, and training. In short without basically understanding the detailed origin of the record, the objectives have been exploratory and correlational. To remedy this, we should greatly increase the amount of controlled experiments on dogs, and relate the pattern of blood-flow and its variation directly to the BCG. The earlier work on volume and force deserves and is getting restudy,[4] with the improved physical and physiologic methods now available, and with increased recognition of the role of arterial elasticity. Such basic work seems essential, to complement the clinical exploration that is bound to continue.

Recording the BCG

In this section we will review the rationale, practice, and critique of specific BCG instruments, of transducers and recorders, and of the aspect of motion selected (D, V, or A).

Ballistocardiographic Instruments, Current and Developmental (Head-Foot): In practice, the direct-body (DB) method is still the most common: to record the displacement of the *shins;* next is the displacement (dynamically equivalent to the DB but more reproducible) of a stiffly sprung bed, called the high frequency (HF) ballistocardiogram. On both methods there has accumulated a large clinical literature. These methods of recording give the impression that there is such a thing as a generally characteristic or "normal BCG" for all healthy people: in the sense that there is a range of "normal ECG" form that changes little with age. This impression arises from a simple characteristic-frequency, which dominates the HF record. This resonance, simply an artefact arising from the passive vibration of dorsal tissues, suppresses many details of cardiovascular activity. More importantly, this tissue vibration happens to agree with and so enhances a certain recurrence time or spacing between events in the IJK complex (Fig. 1), found in most young normals. Departure from this spacing toward either irregularity or another interval, then produces the so-called "abnormal" record. Since this departure from simplicity also increases with age, the BCG fails to separate adequately overt heart disease from normals in later life. With this discovery of many normals with abnormal records, came disappointment with the whole BCG procedure, instead of with the "normal vs. abnormal" method of interpreting the BCG.

The misleading resonance artefact was recognized as early as 1944. To avoid it there was developed (a) a medium-softly suspended, [low-frequency (LF)] bed,[5] and lately (b) the ultra-softly suspended (ULF)[1] bed, used first by Gordon[6] and Henderson,[2] more recently given a rational foundation,[8–10] and now typified by the simple mercury-bed[10] used in the head-foot direction. The ULF bed has several advantages over the HF type. (1) Floor noise

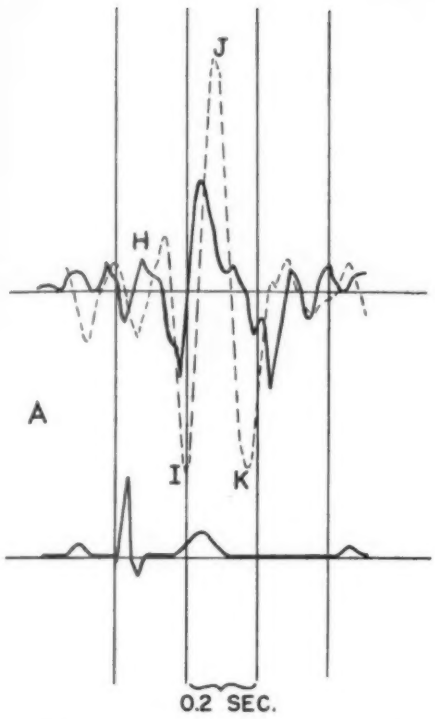

Fig. 1A. *Solid line:* One type of normal BCG with ULF coupling to earth (mercury bed). *Dotted line:* Same subject with HF coupling (Starr bed) showing (a) periodicity of HIJ forces causing resonant peaking and after-oscillation (K wave); (b) phase lag of HF and DB records which defeats temporal correlation.

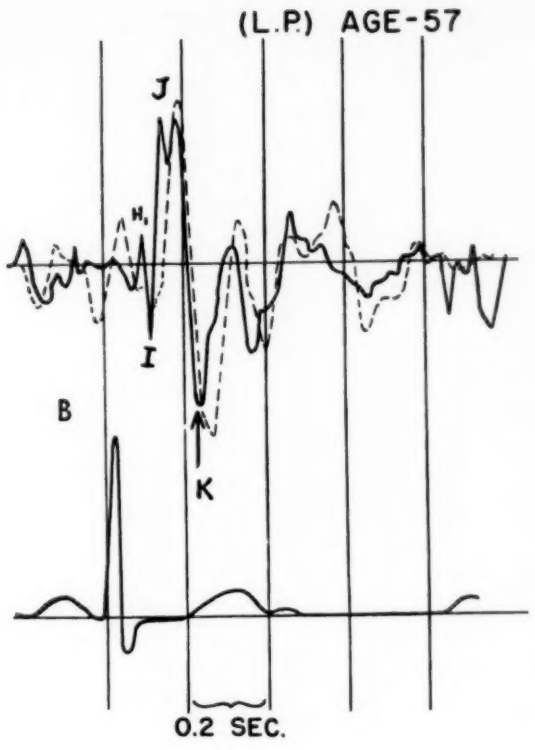

Fig. 1B. *Solid line:* Abnormal (hypertensive) HLF-BCG showing the abnormally sharp HI, a sharply split J, and abnormal occurrence of deep K. *Dotted line:* The HF-BCG of same subject shows no high frequency information or deep splitting; abnormality of K shown only by its width.

is reduced; (2) resonance artefact is removed; (3) the record has a unified physical interpretation for all frequency components; (4) finer details are readily discriminated and rendered with higher reproducibility than from the shin-bar record of body acceleration. The ULF BCG disadvantages are practical (an unwieldy structure, expensive transducers and amplifiers), and insufficient diagnostic experience. Even more importantly, elimination of the resonance frequency also eliminated the false simplicity of the normal BCG described above, so that there still remains to describe new criteria of normals varying with age, as well as to characterize the abnormal and pathological types.

Refinements in Methodology: The methodology of the ULF-BCG is being improved. Some very light stretchers suspended by 6 ft wires have been made available as preliminary models. By adding negative-pendulum pins,[11] the wires are shortened and spurious harmonics reduced, along with the period. A rigid platform on large steel balls[12,13] is found to reproduce the ULF displacement waves rather well, but the acceleration (force) record derived therefrom is inferior. An experimental differential-pendulum bed[14] supported from below, having ultra-low-frequency in both RL and HF, has been in clinical use for some time.* Any of these supports prove satisfactory as temporary devices at the present stage of research.

The weight of the platform should not exceed about $^1/_{15}$ the body-weight; even if the natural frequency is kept "ultra-low," beds heavier than this cannot follow rapid movements of the body. Several such attempts have appeared recently;[15–17] what happens is that the dorsal-tissue springs are activated, giving resonance and mechanical attenuation of the faster body motion. The K wave deepens, the phase of motion lags, rapid discriminatory detail is lost; one sees again the characteristic errors of the HF (bed or direct-body) record.

In general, the period of a ULF bed should be not over 0.3 c/s if one is to record the heart frequency with-

* Described in detail by Scarborough and others elsewhere in this Seminar.

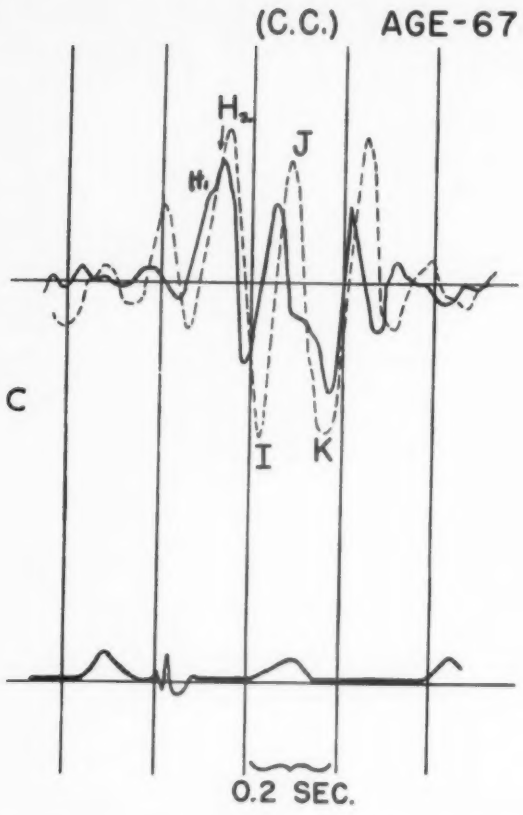

Fig. 1C. *Solid line:* ULF-BCG of clinically normal older subject having abnormal H wave, abnormal JK segment. *Dotted line:* HF-BCG of same; note periodicity exciting resonance, which masks detailed information present in ULF-BCG.

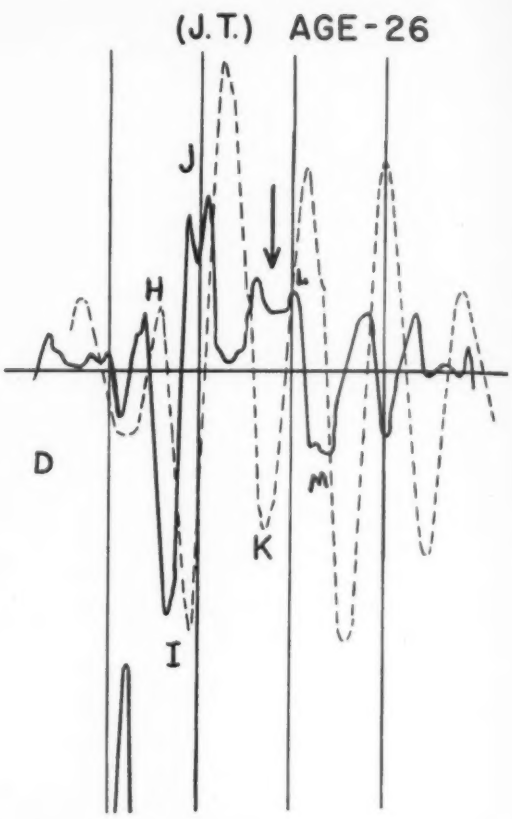

Fig. 1D. *Solid line:* ULF-BCG of young subject with coarctation, showing additional headward force on body in K wave position; split H and J. *Dotted line:* HF-BCG of same, showing slight decrease in K, as well as dominance of periodic artefact due to adventitious agreement of cardiovascular impacts with body-period.

out serious timing (phase) error. Yet at 0.3 c/s the resonant action must be low, to avoid accentuating the strong response to respiratory shift of the blood and liver, which otherwise swamps out the heart beat component. A means of controlling this adequately has yet to be devised, so that held-respiration is used. In some important cases, this practice will radically alter the form of the record; consequently the methodology of the *displacement* ULF-BCG, both as to equipment and application, must be regarded as still in a research stage.

The methodology of the HF-BCG has also been refined, in view of the large clinical literature available. A stable and reproducible Starr bed is available commercially.* The direct-body devices have been analysed as to errors introduced by the shin-bar coupling, and as to ways (DVA system)[18] for recovering the detailed information rejected by the resonant cutoff (beginning at 5 c/s)—which still characterizes all standard HF methods.

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The various HF, LF, and ULF systems have been compared and analysed recently.[10,19]

Attempts to subtract out the HF resonance error seemed promising at first,[20,21] but are not widely used; reasons have been given[9] why this compensation is not successful. Conversely, electrical filters have been introduced in the ULF recording to make it resemble the HF-BCG, but now with a *known* resonance effect. The same principle has also been used clinically with the direct-body BCG: where by mechanically "tuning"[22] the shin-bar coupling, one accentuates selected features of the record. Such purely heuristic practices, if reproducible and fruitful, seem clearly justified at this stage of the BCG problem.

Derivative records with the HF and ULF-BCG: When the force that resists cardiovascular impacts on the body is provided through the dorsal tissue springs (with HF methods), the body *displacement*, y, measures the cardiovascular "force." However, since the body so supported

is *resonant* at the frequency of impacts, the *velocity* y' measures the "force" at these frequencies. At still higher frequencies, when the resistance is provided mainly by the body's *inertia* as in faster details, its *acceleration* y'' (ULF methods) now measures the same "force". So with the HF-BCG to see the force aspect for all frequencies (slow, 4 to 5 c/s, and rapid), one must record all three (D, V, A) aspects of motion for each "lead" (head-foot, lateral, etc.). With the ULF method, a single tracing (the acceleration) gives the force information for all frequencies. The main lesson from the DVA method of recording, is that consistent clinical information of interest may appear in higher frequency records i.e., the higher derivatives prove a means of selectively enhancing certain features.

If the acceleration record alone (with ULF-BCG) suffices, why then get the displacement and velocity too? Otherwise stated, if the D and V records can both be computed automatically from the acceleration, what new information results? It is a peculiarity of the BCG that the displacement ULF record shows so little high frequency detail, and the acceleration record shows so little low frequency, that the derivative and integral records look quite different. A different *physical* interpretation applies as well (v. infra). (This principle applies also to the ECG: taking the spatial slope or gradient of the ECG potential distribution, gives quite new results.)[23]

Frontal-Plane Ballistocardiography and the Coupling Problem: To record reproducibly the details of the whole-body motion in the head-foot (y) direction, requires a strong connection between the body and its support, whether by HF or ULF method. In head-foot motion, a footboard provides this tight coupling; but in lateral motion, a patient lying on a flat bed executes a rolling motion under cardiovascular forces, even when "chocked" at thorax and hips. This roll produces two types of artefact in the RL (x) motion of the support: errors which so far have prevented recording an acceptable BCG component in the lateral direction—although some attempts have been made.

These superimposed errors are (a) a true axial *roll*-BCG, generated by the blood motion which operates on the support in such a way as to reduce, cancel or even to reverse the *translational* RL-BCG being sought; (b) a resonance in body roll (precisely analogous to that in the head-foot mode), which is generated by any bed or support (e.g. pendulum, mercury, balls, stiff spring) which cannot roll freely about a longitudinal axis. This roll resonance furthermore produces a sharp cutoff and/or peaks of the BCG information at a mid-frequency.[24] It results from both errors, that all the current lateral (x) BCG's not only accentuate one frequency, but also distort or reject the sharp details normally found on the *y* component of body motion.

A number of lateral BCG records have been published, as obtained from both HF[25] and ULF[26] platforms. Because of the strong roll-artefacts involved, their comparison between patients is really unjustified. This stringent conclusion is supported also by BCG studies using subjects in prone and supine posture.[14]

Although intrinsic resonances prevent getting correct lateral (RL) BCG records from any HF system, a proper ULF system can give them. This may be done by allowing the patient's support to roll freely, and recording the simple lateral motion of the gimbals. Such supports are being developed.[24]

Ballistocardiographic Vectors in Translation and in Rotation: The anterior-posterior (z) BCG has been recorded from high-frequency support of the thorax[27] or of whole body[28] much as is done in the (y) direction; so that if one accepts the resonance error the sagittal-plane projection of the HF-BCG vector can be shown. However, ULF recordings in the (z) direction have not yet been made, though progress in this direction is good.

The *rotation* of the body under BCG forces has been studied[29] but the difficulties of freeing it from translational admixtures, and of separating out the pure rotational-force component are great. So far, there seems no good reason for expecting enough unique information from the rotational vector to justify the added complexity.

TECHNICAL ASPECTS

Calibration, Transducers, and Recorders: Since it has been agreed that the BCG ordinate be given in motion units (rather than force), calibration reduces to impressing a known motion on the support. If the transducer is stable, a simple electrical signal suffices thereafter.

The *transducer* problem is not yet solved satisfactorily. The simple velocity-pick-up[30] can be used only in extremely quiet locations, because it senses building vibrations, greatly enhanced in the derivative (acceleration). The commercially available seismic-reference class

(accelerometers) are expensive and require much more gain than is available in an ECG amplifier. Of the stable (bridge) group, the inductance type* gives the best output and signal-noise ratio. In the self-generating class, piezo crystals are stable neither thermally nor in low-frequency response, a serious objection. The mercury-stack[31] is promising, but not yet perfected as to stability either of gain or low-frequency cutoff.

The *choice of transducers* (devices to convert motion to electrical voltage) depends partly on the amplifier and recorder system selected. Present evidence that two or three BCG axes will be essential, warrants multichannel recording. In addition one should record respiration and also identify the wave details by a timing trace, ECG and/or heart-sounds, because of the important BCG events just before diastole. The simplest and minimal adequate equipment would consist of four channels of recorder of the photogalvanometer type with immediate display (zerox or ultraviolet traces), resistive bridge accelerometers and chopper preamplifiers. More standard equipment, and so somewhat cheaper, would comprise pen-recorders (ink, thermo, carbon) inductance-bridge accelerometers and carrier amplifiers. For BCG research with dogs, or for ULF-DVA on two or more axes, at least eight channels are needed; in which case the photo-galvanometer records are much more economical. (Space forbids a discussion of the optimum compromises in system design.) It should be apparent that without technologically well-established methods we are dealing with a research tool at present, rather than one ready for clinical practice.

Biophysical Aspects of the BCG Record

Until recently, the major emphasis of ballistocardiography has been on the "ballistic" effects observed: forces, impacts, recoil, velocity, and momentum patterns of body and blood; and to a lesser degree stroke volume and respiratory displacement. The work of Burger[19] and of Noordergraaf and others[34,35] on plethysmographic aspects of the BCG has enriched the physical basis and raised our expectations that the BCG waveform can be explained physiologically in detail.

It is a mistake, however, to think that whatever is recorded refers to motions, momenta and forces in the cardiovascular system: we must make due allowance for body ballistics. This was proved by the radical change in form, timing and detail that appeared when the artefacts and distortions of direct-body recording were overcome (ULF vs HF-BCG). In like fashion, the practice of regarding the product of the support-acceleration × whole-body mass as a measure of cardiovascular "force" has very weak foundations. Much scattered evidence exists, that the BCG components above 8 c/s include appreciable phase and amplitude alteration, due to breaking up of the body mass into independent oscillators. (Curiously enough, the heart itself is not one of these.[39]) From this breakup it does not follow, however, that BCG components as high as 20 or 30 c/s have no clear physiologic[32] or clinical[22] significance. Such significance indeed has been evidenced, but would be improved by methodology which reduces the various kinds of distortion in the important faster components.

In this direction go the use of thoracic recording[33] and of BCG chairs[24] to further unify the body and couple better to it; more attention to relation of center of gravity to location of pickup; and to coupling between modes (e.g. roll to lateral). For these reasons, one cannot realistically expect a standardized BCG methodology at present. It is a long step from realizing the nature of an error, to developing a successful biomechanical remedy. In this process, theoretical and basic work still interweave with the practical.[24]

Internal Mechanics

We may turn from exterior to interior ballistics, and consider the arguments by which the recorded body-motion can be interpreted to measure *cardiovascular* mechanics. Noordergraaf's[34] direct evidence that the displacement BCG (ULF) is a "plethysmogram," has now[36] been extended to the acceleration record. Blood acceleration, however, depends intimately on vessel elasticity and tortuosity. This is because the heart pump distends, elongates, and drags the vessel walls, in addition to accelerating the flow axially. Simple distension and blood acceleration are shown by Noordergraaf to account for the simpler (youthful) BCG. However, in later life, non-linear distension (hardening), arterial elongation and viscous drag on arterial walls affect the particle and pulse velocity, and consequently the spatial distribution and direction of the component accelerating forces. The contribution of the large veins to the D and V aspects, was omitted also

* Northam Electronics, Inc., Altadena, California.

in this analysis. Thus while we may expect to see regular sequences of BCG waves at early and late systole, in the events so grouped, variable components go into their summated amplitudes.

With the QRS complex of the ECG we relate changes in form to abnormal summation of elements in the depolarization cycle and in the T cycle which follows. So with the acceleration BCG (ULF), we start with an atrial complex (fg), then an ejection complex (hij), a closure complex (klm) and a diastolic complex (mno). Each complex of waves has distinct characteristics, jogs, ratios and relations to the others, which are the basic BCG data. These likewise represent summation of local forces. As with modern reading of the ECG, classifications of the BCG into "normal-abnormal" should give way to more detailed understanding of these separate complexes.

Other articles in this series will describe more fully our current understanding of the physiologic basis of these BCG complexes. In general, the presystolic complex (fg) comprises atrial and ventricular filling action, and is sensitive to AV valves and venous return. The early systolic complex (hij) might better be called "arterial filling complex," as by mid-systole the pulse rise reaches the iliacs and arterial elastic effects on blood acceleration begin to appear. The third segment (klm) of interest in acceleration begins in late systole and ends well into diastole, associated with but preceding the *falling* limb of the pulse wave. Well before aortic valve closure, the blood reverses acceleration; but this terminal pattern of momentum change is not fully communicated to the body till well *after* closure: at the arch (l) and iliacs (m). (This illustrates the fallacy of completely accounting for BCG events in early diastole, by mitral and filling action, based solely on temporal correlation.) The fourth or diastolic complex (mno region) covers the mitral valve opening and filling from the cardiac aspect. There are also vascular aspects, such as (in the limbless) periodic waves due to reflection,[33] absent in normals.

There is great need for systematic research in the analysis of these four major complexes of the head-foot (ULF) BCG. Pharmacologic aids[32] are proving useful in identifying the mechanisms most active at each stage. Pathology should help.

Energetics of the BCG

The above deductions about blood motion (plethysmography) and acceleration as affected by heart and vessels, rest on fairly convincing grounds. However, deductions[33,37] regarding cardiac energy, work and power seem less so. Unlike the *moment* and the *momentum*, which are equal for blood and body, the *kinetic energy* (K.E.) of the body in the BCG picture is only 0.1 per cent that of the blood at most, and this fraction varies greatly during the cycle. Moreover, most of the energy of cardiac contraction goes into distending vessels during systole, and little appears in K.E. of blood (or body). So the K.E. of the body motion proves a poor measure of cardiac work or efficiency. Again, cardiac "work" is not properly measured by BCG "force" $\times$ body displacement, since these factors are in opposite directions much of the time. Similarly, the "power" involves out-of-phase components whose product is not simply force $\times$ velocity. Finally, these products, taken over a heart beat, do not apply to the ventricular output, because so much of the BCG cycle describes other cardiovascular action than ejection. If eventually we can deduce cardiac work from the BCG, it should be based on more exact vector values taken over that very limited part of the cycle dominated by ventricular contraction. These vector values, it has been shown, cannot as yet be recorded as curves whose physical meaning is sufficiently similar to warrant multiplying their ordinates.

Conclusions

Even with modern technology, the special problems of recording the BCG without gross mechanical error have not yet been solved. Part of the difficulty is in engineering, to realize the extended rigid yet light structures required, and to invent ways to suspend the body with the required freedom from earth in six modes of motion. The main difficulty has been conceptual, to realize the nature of the mechanical components, forces and couplings involved, and the approximations admissible. Given reason-

ably true and physically homogeneous records of the motion then (as with the ECG) one can proceed to study vector projections (e.g., frontal plane). Before this, of course, there is no objection to observing the body motions by any simple means available and deriving clinical correlations. But this should not create expectation that any of these means should be adopted as standard, however widely used, if they prove incompatible with the goal: which is to record all the translational BCG components with such mechanical similarity in each axis, that they combine legitimately with each other as vector components. Though at this stage it is more difficult to achieve than with the ECG, there is no reason as yet to doubt this goal. Meantime, full consideration must be given to validity of the approach, approximations accepted, and the dynamic laws governing complex extended bodies.

Equally important is it to grapple with the hemodynamics of the heart and vessels, an extremely labile system. With observations properly designed and conducted, a complete static and dynamic BCG examination should eventually give much information about cardiovascular status and reserve. We have not begun to scratch this possibility. Prior to this goal, we need extensive studies with dogs and humans: on the patterns of pulsatile flow, motions of body parts, local changes of driving momentum throughout the cycle—as affected by physiologic and pathologic ranges of cardiovascular operating states. Realization of stable dog preparations,[38] whose BCG compares with the human, should greatly aid this line of advance.

In electrocardiography, only after 40 years of clinical use are we barely beginning to understand the intimate details of depolarization, and the curious vector impedance pattern which determines the surface potentials. So with ballistocardiography, clinical application may need to continue for years before what is observed is fully understood in terms of biophysical mechanisms. Nevertheless, it is the interest and support of those using the results that carries the long years of basic research. It seems incumbent therefore on research workers occasionally to communicate their perspective: the sense of important possibilities and the fact of strong progress in both methods and understanding, which are now so real to scientists in this field.

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On Reading Ballistocardiograms*

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THE PURPOSE of this brief presentation is fourfold; to explain the relationship of the different types of ballistocardiograms to one another, to relate how ballistocardiograms are being taken and interpreted in our laboratory, to warn against certain sources of error which I fear are often overlooked, and, finally, to indicate very briefly my present opinion of the direction of greatest promise of the method.

RECORDS FROM DIFFERENT TYPES OF INSTRUMENTS

Needless to say, the record secured will vary with the type of instrument used and with the information recorded by the electrical circuits used. The ability of electrical engineers to provide circuits which yield the velocity or acceleration of the motion picked up, or its integral, has resulted in a wide variety of ballistocardiograms[1–7] mathematically related to one another through the calculus. Figure 1, taken from a previous publication,[8] will help readers to see the relation of one kind of record to another. In this laboratory we have had far more experience with force ballistocardiograms than with any other kind, and the discussion which follows will be centered about records of this type.

ON TAKING THE RECORD

Ballistocardiograms record physiologic events which vary with the physiologic condition of the patient, so to obtain the maximum information one needs a record taken under standard conditions. These have usually been defined as after 15 minutes' rest and not within two hours after a meal.

One of the chief hazards of ballistocardiography is the frequent appearance of artifacts in the record. With good apparatus and skillful technic these can be minimized, and it is important to reduce them to as low a level as possible. Thus artifacts arising from movement of

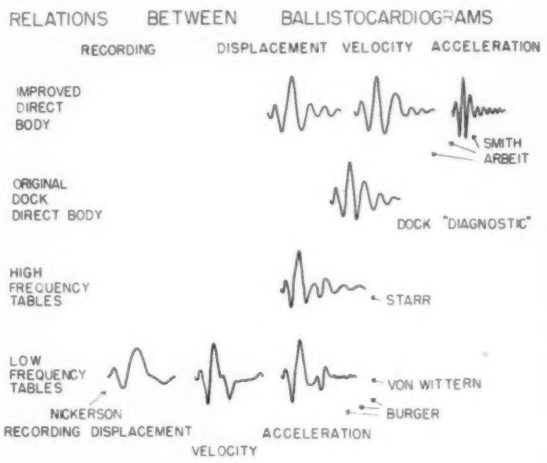

Fig. 1. To show the relation of the records of one type of ballistocardiograph to another. Vertically aligned in the center is the "force ballistocardiogram" in which the record is one of force. This is secured either by recording the *displacement* of a *high*-frequency table, or the *acceleration* of an *ultra-low* frequency table. Shin-bar records, when displacement is recorded, are essentially force records also. Various authors are now interesting themselves in records of other types. Thus, Arbeit,[4] and Smith,[5] by recording the velocity and acceleration of shin bars secure the records shown on the upper right, while those interested in low-frequency instruments, by recording displacement and velocity,[1] get records like those shown at the bottom left. The original Dock technic, though designed to record displacement, probably gave a record lying between displacement and velocity and so it has been placed somewhat out of line with the true force records. (From: Starr, I.: in *Diagnosis and Treatment of Cardiovascular Disease* (ed. by W. D. Stroud and M. W. Stroud.) F. A. Davis Company, Philadelphia, 1957. Reproduced with the permission of the author and publishers.)

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the patient can be minimized by having the patient relaxed and comfortable at the time of the tests. Reassurance may be most important; most hospital tests involve pain or discomfort and the patient may be tense from apprehension. Small adjustments of the headrest may greatly contribute to his comfort and cause him to relax. A few friendly words may make the difference between a tense patient giving a record full of artifacts, and a relaxed patient giving a perfect record. A second test after the totally innocuous nature of the procedure has been realized may be necessary.

Under certain circumstances special steps may have to be taken. If dyspnea is severe, respiratory impacts may destroy records taken in the usual way. The newest high-frequency ballistocardiograph in our laboratory can be tilted to 40° and used to get satisfactory records in orthopneic patients. Occasionally, in records taken with the patient level, the inhalation of oxygen permits so much quieter breathing that clear cardiac complexes can be secured. In Cheyne-Stokes respiration fine records can be secured during periods of diminished breathing or apnea. We often ask dyspneic patients to voluntarily over-breathe and then have gotten good records in the period of lessened breathing which followed. By simply watching the patient and taking the record when respiration is at a minimum, a better record can often be secured.

The number of patients in whom no satisfactory ballistocardiogram can be obtained is very small, but despite the best of apparatus and technic artifacts are present to some degree in almost every record. One of my greatest concerns is that they will be mistaken for evidence of cardiac abnormality by unwary doctors. Let us, therefore, carefully consider the different kinds of artifacts to which these records are subject, and discuss the means of identifying them so that errors of interpretation may be avoided.

Interpretation of Ballistocardiograms

Identification of Artifacts

The first step is to identify the artifacts which may be divided into five classes according to their origin.

Respiratory Artifacts: These may be seen to some degree in many normal force ballistocardiograms, the effect being limited to slight arching of the record's base line. Such respiratory

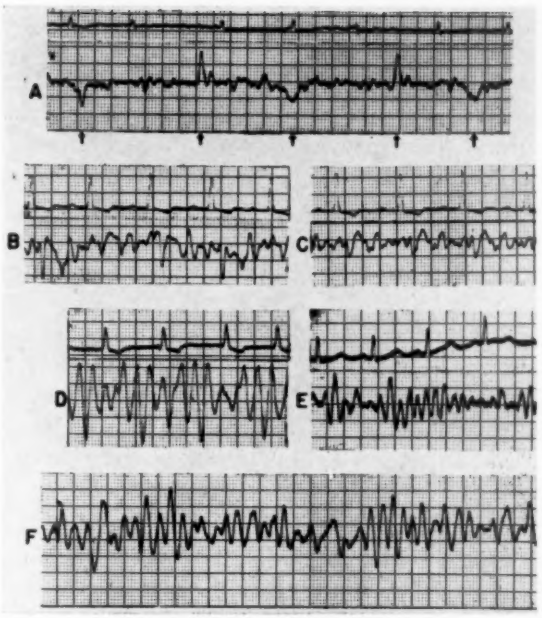

Fig. 2. Artifacts occurring spontaneously in force ballistocardiograms. (B) and (C) are from an ultra-low frequency instrument; (A), (D), (E), and (F) from a high-frequency table. (A) Respiratory artifacts which stand out clearly because the ballistocardiogram is very small. Note "respiratory arching" of the base line as well as sharp headward and footward waves when the diaphragm changes its direction over the arrows. (B) Respiratory arching and artifacts which, when superimposed on ballistocardiograms occurring simultaneously, gravely distort them. (C) Same subject as in (B). Record taken a few minutes later when he was breathing less violently. In the absence of respiratory artifacts, the consistent systolic pattern is clearly seen. After observing (C), one should look again at (B) and note the distortion of some complexes. (D) An example of resonance. After-vibrations, probably from movement of the body on the table, fill diastole. No proper interpretation can be made of a record of this kind. (E) Temporary resonance distorts the second systolic complex, but then quiets down. We do not know what was set into vibration, but the interpretation must be based on other areas of the record. Note that the preceding and following systoles are free of this trouble. (F) This is a record taken immediately after smoking one cigarette. Note the complete confusion; it is very difficult even to say where systole is. One has no right to interpret this record as indicating disintegration of cardiac function. Nothing is repeated, and "nothing not regularly repeated is worthy of attention." In all probability, the patient was trembling and the true ballistocardiogram is confused by a multitude of artifacts. In the next record taken $2^1/_2$ minutes later, the multitude of artifacts had disappeared, and a clear record of cardiac complexes was obtained.

effects are greatly increased in the types of records illustrated on the left side of Figure 1, while those records found in the right of the figure are free of this difficulty. When displacement of an ultra-low frequency ballistocardiograph is recorded, the record on the extreme left of Figure 1, the effects of normal respiration so overshadow the cardiac effects that most of these records must be secured while the breath is held.

When respiration is abnormally vigorous, not only is the arching in the force ballistocardiogram more marked, but artifacts, due to the forces developed whenever the diaphragm changes its direction, appear. Figure 2 gives examples. These may be mistaken for cardiac complexes or they may distort any complex of cardiac origin which occurs simultaneously, so they must be identified as artifacts or errors of interpretation will be made. A record of respiration is a great help, but to secure such records routinely by a mechanical method is not worth while. In this laboratory we regularly mark the records by observing the chest, pressing a button during inspiration, and releasing it during expiration. Due to the observer's reaction time, this mark is always somewhat late but, by making allowance for the delay, the position of respiratory artifacts is easily identified and this simple method suffices for routine work.

Violent breathing may so totally disrupt the force ballistocardiogram that the cardiac complexes can hardly be identified. Methods of securing a satisfactory record under such circumstances have been described.

Artifacts from Movement of the Subject: Such movement causes artifacts even though it may be so small that it escapes attention. Gross movements produce forces much larger than those of normal cardiac complexes, and so they are readily identified, but small movements may produce forces about the magnitude and frequency of true physiologic ballistocardiograms and some may be easily mistaken for extrasystoles, or, superimposed on the waves of cardiac origin, may cause the appearance of abnormal contractions.

Much more difficult to identify are the distortions due to the minute muscular movements which occur in patients whose muscles are tense, as with apprehension. These distortions are seldom large enough to obliterate the cardiac complexes but they confuse them by superimposing notches and slurs.

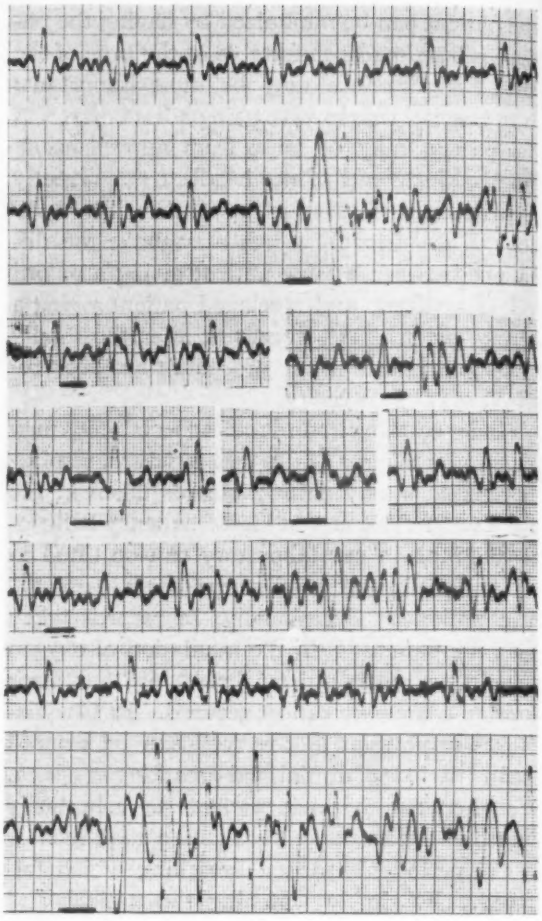

Fig. 3. Artifacts produced experimentally in one healthy subject. The top record is as free of artifacts as most records are. In the lower records, at the mark, the subject made various movements which affected the record immediately following in various ways, depending on the magnitude and direction of the movements. Some of the record distortion which resulted might well be taken for cardiac abnormalities by the unwary. At the mark on row 5, she was told to talk and took a deep breath before doing so. Row 6 shows, on the right side, the high-frequency vibrations due to motion in the building. In row 7 the subject at the command began to breath violently. Note that the record of cardiac events is completely destroyed. From: Starr, I.: *J.A.M.A.* 155: 1414, 1954.

In Figure 2 we give examples of artifacts due to movement of the subject found in records taken routinely, and Figure 3 gives examples of similar artifacts produced experimentally.

Artifacts due to the subject's movements, ap-

pearing spontaneously in routine records, are usually easily identified by the fact that they are not regularly repeated and so break up the record in an irregular manner. I cannot too strongly emphasize the rule of this laboratory for reading ballistocardiograms: "Nothing not regularly repeated is worthy of attention." But before applying this rule the reader should be reminded that, in a ballistocardiogram containing abnormalities of form, one complex is seldom exactly like those adjacent unless the breath is held. So, in records secured during normal breathing, one seeks identical abnormal forms, not in adjacent complexes, but in complexes occupying a corresponding position in other respiratory cycles. A single abnormal complex is always to be considered as due to an artifact until the reverse is proved.

Artifacts from Movements of the Building: These are a frequent source of difficulty. We had such trouble whenever a trolley passed on the street, although it was eight floors below us, and when the elevators started or stopped abruptly. More serious were vibrations due to motors in nearby rooms.

These building vibrations, of high-frequency, have little or no effect on the records shown on the left side of Figure 1, but for those on the extreme right they must often be a most serious problem.

Needless to say, every effort should be made to keep building vibrations out of the record by mechanical means, but this is not easy. High-frequency ballistocardiographs or tables used for shin-bar methods need firm contact with the floor to provide the necessary inertia. In our ultra-low frequency instrument building vibrations often enter the record through the support for the coil. Our efforts to completely isolate our apparatus from building vibrations have never been completely successful so we have learned to recognize and avoid the parts of our records so distorted.

Such artifacts usually manifest themselves by a series of waves of much higher frequency than the main waves of the ballistocardiogram, a fine vibration best seen in the flat parts of the record and causing notches at the tips of the waves which may be mistaken for a physiologic abnormality by the unwary. Usually the identification of such artifacts is not difficult; such fine vibrations are not seen in normal records and those due to street traffic and elevators are not continuous, superimposing themselves on the ballistocardiogram for a few seconds and then, for a while, the record is free from them. One soon learns to recognize such spots and to interpret the record by studying other areas.

Artifacts from Interference: Such artifacts must always be kept in mind as a source of error. In records secured by any instrument, if the pulse rate is very rapid, the terminal group of waves of any systole (L, M, and N) may be overtaken by the initial group (H, I, and J) of the systole following, and the superimposition of the two wave groups prevents proper recording of the systolic forces. Therefore, ballistocardiograms taken in extreme tachycardia must be interpreted with great caution. Figure 4 gives a good example of such interference.

Resonance Artifacts: Even when the pulse rate is within normal limits one occasionally encounters a ripple of after-vibrations persisting until the next systole and distorting its record. Examples are shown in Figure 4. In our old high-frequency instrument this artifact was probably due to movement of the body on the table, which, set into vibration by the preceding systole, persisted into diastole.

Resonance of this kind is the chief difficulty of the shin-bar methods as they are usually employed, for after the body has been deflected by the cardiac forces, for a brief period it rocks back and forth on the surface on which the subject lies without any other force being applied. These after-vibrations prevent the proper recording of the terminal ballistic forces, usually by deepening the K and magnifying the L waves; and, if they persist until the following systole, they distort the record of its forces. The newer developments of this technic,[9,10] which seek to dispose of this error by electrical means, greatly improve the record, but at the moment they are difficult to carry out. Even in ultra-low frequency force records, essentially free of the difficulty occasioned by resonance from movement of the body on its surroundings, resonance occasionally appears, perhaps due to some movement within the body.

If any record, no matter how obtained, shows

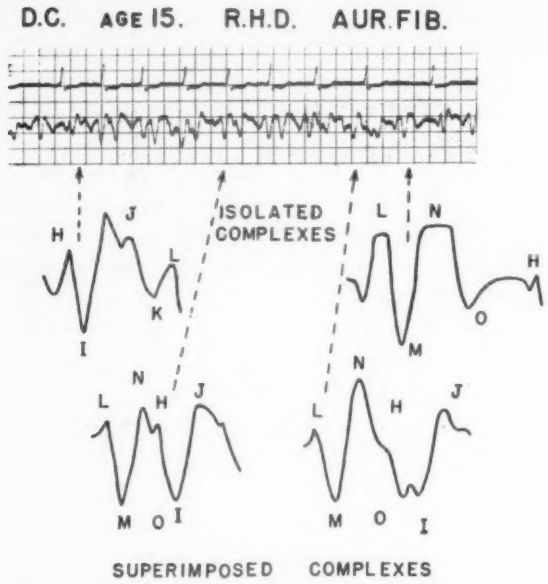

Fig. 4. An illustration of interference. During the longer cycles of the arrhythmia, the record of the terminal complexes is completed before the onset of the following systole, so the ballistocardiogram of this systole is undistorted. But when the cycle is short the terminal complex of the preceding systole is superimposed on the initial complex of the systole following, and distorts it badly. Initial and terminal complexes, both distorted and undistorted, are enlarged below to emphasize the difference.

rhythmic vibrations which persist until the following systole, it is wise to refuse an exact interpretation of it. We ask the patient to return for another test in the hope that a more satisfactory record will be secured. As apparatus has been improved, and since our patients have been more tightly attached to the high-frequency table, such resonance has caused less and less trouble in this laboratory.

TIMING THE RECORD

Identifying the Onset of Systole: The artifacts having been identified, one turns his attention to the location of the ballistic waves in the cardiac cycle. Their identification as H, I, and J waves, etc., is perfectly obvious in records secured in all healthy persons and perhaps 95 per cent of patients. Sometimes, however, one may be uncertain, and, in a few cases, badly mistaken. Therefore some other method of placing the waves in the cardiac cycle is very helpful in the occasional case; in our laboratory this is either a simultaneous electrocardiogram or pulse wave, when we have a two-channel recorder available. When only one channel is available a circuit which permits superimposition of electrocardiogram and ballistocardiogram is very useful, the electrocardiogram being reduced in amplitude until only the R wave can be identified as a spike on the ballistocardiogram. Only a portion of the record should be taken with the two superimposed to establish the time relations; interpretation of the ballistic form can then be made from the remaining part, and errors of interpretation, due to distortion of the ballistocardiogram by the electrocardiogram, avoided.

Identifying the Waves: The location of the onset of systole permits one to divide the ballistocardiogram into two parts, the initial group of waves (H, I, and J waves), and the terminal group (L, M, and N waves). The amplitude of the initial wave group, produced by the forces as the blood accelerates, reflects the cardiac strength and this has been the group most studied, and so, in interpreting the records, one pays most attention to it.

The terminal group of waves is well shown only by the most modern technics. It is clearly seen in the force records from ultra-low frequency instruments (when acceleration is recorded), and in the force records from the best high-frequency instruments (when displacement is recorded) provided the subject is tightly attached to the table. In records from the original high-frequency instrument used in this laboratory, the terminal group was distorted by after-vibrations from the much larger initial group. I have never seen a terminal group well recorded by the usual shin-bar technics, but electrical neutralization of the artifacts brings it out.[9,10] Because of these difficulties the significance of the terminal group of ballistic waves has been little studied by clinicians hitherto. However, two things need to be said about this group of waves. In an occasional abnormal record, the waves of the terminal group may exceed those of the initial group in amplitude, and it is in such records that, relying on inspection of the ballistocardiogram alone, one may be badly mistaken concerning the position of systole and go completely wrong in identifying individual waves. Finally, though the terminal group usually occurs early in diastole, at the time when

maximal filling of the heart is taking place, recent evidence relates its origin, not to the forces inherent in cardiac filling, but to those due to deceleration of blood, accelerated by forces of the preceding systole, in the peripheral arteries. This event is found in diastole because of the time required for the pulse wave to reach the extremities. So, unlike the initial group, the amplitude of the terminal group is not directly related to the strength of the cardiac contraction.

Time Relations of the Waves: Having located the onset of systole by means of a simultaneous electrocardiogram or pulse tracing, and identified the ballistic waves, one can consider the time relations of the ballistic waves to the other events of the cardiac cycle. Normal standards defining exact time relations between electrocardiogram and ballistic waves are available, but as yet we have made little practical use of them. One reason for our hesitation lies in the fact that the relation between deflections of the electrocardiogram and the onset of mechanical systole is not as clearly defined as most doctors seem to think; waves given the same letter in different leads are often not identical in their timing, and the time relations between the electrocardiogram and mechanical systole in heart disease have been but little studied. Therefore, when time relations between electrocardiogram and ballistocardiogram are found abnormal, one does not always know in which record the abnormality lies. When one uses a pulse record to time the onset of ejection, allowance must be made for pulse wave velocity, which varies from subject to subject. For these reasons we have been content with the detection of large abnormalities by inspection and we make no time measurements routinely. But marked delay in the appearance of the ballistic waves is regarded as evidence of poor myocardial function.

THE AMPLITUDE AND STANDARDS

Needless to say, differences in amplitude have no meaning unless one has a method of calibrating one's record and in this laboratory we are not content unless there is a calibration on every record. Not only does this make the record's amplitude have meaning but it provides an invaluable safeguard against unexpected faults in the apparatus. To see a series of square waves made by a known force on any record not only provides a calibration, but assures one that the instrument was in proper working order when that record was taken.

With experience the normality of the amplitude of most records can be estimated at a glance. In some records measurement is necessary. The vertical distance between the tips of the I and J waves provides the simplest criterion of record amplitude, but it is better to use the sum of the areas of the I and J waves. Both these values vary with the respiratory cycle. However, it is not necessary to measure a long series of complexes; our routine technic is to select by inspection one typical large and one typical small complex of the respiratory cycle and to measure only these. The average of their amplitudes is very close to the average amplitude of large numbers of complexes.

Standards Applied to Different Instruments: With such a measurement of amplitude before one, one seeks to determine its normality by means of normal standards. Here two difficulties arise, one technical, one philosophical. No instrument being altogether perfect, it cannot be assumed that standards prepared from records secured on one instrument will surely be applicable to records from another. Thus force records from the original high-frequency table constructed in 1936 have a somewhat greater amplitude than records secured on the newer high-frequency instruments when the subject is tightly attached to the table. Force records from our ultra-low frequency instrument are somewhat smaller still in maximum amplitude but closely similar in I and J wave area. As instrumentation has improved such differences have diminished. But at the moment it seems wise to recommend that everyone prepare a normal standard for his own instrument. In making such a standard, experience to date[11] suggests that the sexes should be considered separately, making one normal standard for men, another for women. If this has been done an adjustment for differences in the size of the subjects is of little value, when high-frequency instruments are used. In contrast, in the interpretation of records from ultra-low frequency instruments, the weight of the subject is of prime importance in any quantitative work, unless a

special technic is employed to neutralize differences in weight. In our data[11] taking the square root of the record amplitude or area of the I and J waves produced a more homogeneous normal population than taking the amplitude itself.

Standards as Related to Age: The philosophical problem is concerned with the question of the proper standards to use. If one takes results secured in healthy young adults as defining normality, then a considerable number of persons over 50 years of age, healthy by all present methods of testing them, will be judged abnormal. On the other hand, if one makes a normal standard for each decade of life, one runs the risk of including certain persons with latent heart disease which may unduly depress the values unless they are weeded out by following the series for a long time. When this challenge is met by prolonged followup, it is still evident that the ballistocardiographic amplitude diminishes with age, although health commensurate with age is retained. But one now has the difficulty that those who, in later life, have maintained the cardiac vigor of their youth, may be judged abnormal because their amplitude exceeds the limits of the ordinary person of that age.

In this laboratory there is a slight preference for using standards based on healthy young adults for all subjects, in the belief that the aging of the heart would be better shown thereby. Surely in most people, physical strength, such as could be measured by the ability to lift weights, diminishes as one grows older, and it should occasion no surprise that what is obviously true of the peripheral muscles should be true of the heart also. But surely the relation of the age of the heart to our chronologic age is a matter of importance to clinicians.

ABNORMALITIES OF FORM

The ballistocardiogram of healthy young adults is extremely consistent in form, and this is a most important feature of the field. This form being well known to the observer, deviations from it are easily detected by inspection of the record, the observer looking for abnormal or absent waves, abnormal notches or slurs, and an abnormal relation of wave sizes to one another. The normal wave relations of our instrument have been carefully defined, but we do not yet know how to apply such quantitative information and so we are usually content with simply noting gross abnormalities.

A few further comments should be made. The observer must be familiar with the normal appearance of the record taken by the type of instrument used. The normal H and I waves are quite similar in all types of records. In the ultra-low frequency force records, the K wave is absent or shorter and the J wave shorter and broader than in high-frequency force records of the older types,[6] or in shin-bar records. Force records from ultra-low frequency instruments taken in healthy young adults often show small notches in the H wave, the H-I segment, near the tip or on the descending limb of the J wave, which are absent or less prominent in former types of records. These notches are attributed to normal asynchronism of forces from the two sides of the heart.[12] It is an exaggeration of this asynchronism which is abnormal, not the asynchronism itself.

Shin-bar records tend to give a diastole more or less filled with a damped vibration like that seen in cadavers when a force applied in one direction is released. In interpreting these records it must always be remembered that these after-vibrations are not records of cardiac forces, and that they are sure to distort the record of simultaneous forces of cardiac origin. Usually these after-vibrations exaggerate the K wave, and obliterate the record of the terminal forces. Usually they are damped out before the next systole begins, but if not they distort this record also. Nevertheless, the difference between normal and many abnormal ballistocardiograms is so great that it can be readily recognized in shin-bar records despite these obvious disadvantages.

Inspecting the record for abnormalities is easy for any one who has had enough experience with records secured from healthy persons, and the decision that a record is normal or abnormal in form is also usually easy, though some records should be classified as borderline. But exact rules, though they are contained in my statistical studies, are hard to apply, and I do not know enough to be dogmatic. The common abnormalities of form have been reproduced experimentally, as is described in another part of this symposium, so their genesis seems well under-

stood. But various combinations of the basic types result in so much variety that a brief description of the abnormalities to be encountered in the clinic is impossible. With a single hint I would like to leave the matter. As my experience progresses, I find myself looking at the I wave with more and more attention; by its depth and the slope of the descending H-I segment, we have the right to judge the initial acceleration of the blood, what I think of as the "snap" of the cardiac contraction, which might well be lost early as the muscle weakens.

Methods of Assessing and Interpreting Abnormalities: One can sometimes secure insight into the interpretation of certain abnormalities of form by observing the changes which occur during the respiratory cycle. Thus when the J wave is notched, an abnormality reproduced in cadavers by asynchronous injections into the aorta and pulmonary artery, we find it interesting to try to ascertain whether the delayed wave pertains to the right or left side of the heart. This can often be discovered by a study of the changes in ballistic form taking place during the respiratory cycle. When inspiration begins the right heart is better filled immediately, the left not for an appreciable interval. Therefore, if there are two peaks on the J wave, the one which increases in amplitude immediately after the onset of inspiration can be identified as having its origin in right ventricular forces.

Clinical experience would seem to support the general proposition that the more the ballistocardiogram differs in appearance from the normal the worse off the heart is, but exact information on the significance of particular deviations from the normal has been hard to attain. Two very rough methods of assessing the severity of the cardiac abnormality deserve mention. In this laboratory the ballistocardiograms of aging persons have been followed for periods up to 20 years. In subjects slowly losing normality, abnormality of form is first seen in the smallest complexes of the respiratory cycle and then, with the passage of time, the abnormality spreads to adjacent complexes until all are involved. Hence the proportion of abnormal to normal complexes is considered an important index of the severity of the cardiac involvement.

Another useful set of criteria was proposed several years ago by Brown *et al.*[13] and it has been widely used. We employ a slightly simplified version. In stage II the respiratory variation is increased, the smallest complexes of the respiratory cycle being less than one-half the amplitude of the largest. In stage II the smallest complexes are abnormal in form. In stage III all complexes are abnormal. In stage IV the disorganization is so great that the position of systole cannot be identified from the record. We have reservations about the significance of stage I, for many normal subjects, by voluntarily overventilating, can make their records abnormal to this degree, but we have found these simple criteria very useful.

Practice in reading ballistocardiograms could be obtained from inspection of typical records received with different types of instruments in healthy persons and in those with abnormalities. In Figure 5 are shown normal, borderline and abnormal BCG tracings taken by the high-frequency table. The legend of this figure describes the features of each degree of abnormality that I would dwell on.

Utility of the Ballistocardiogram

It seems appropriate to end this essay on reading the record with a very brief description of how, in this laboratory, we are using the information secured.

Table I is concerned with the three aspects of myocardial abnormality which may be detected by a ballistocardiogram: abnormalities of strength, coordination, and reaction. The detection of cardiac weakness, indicated by a record too small in amplitude, is placed at the top.

TABLE I

Information Secured by the Ballistocardiogram

I	Detection of cardiac weakness
II	Detection of cardiac incoordination
III	Demonstration of normality or abnormalities of cardiac responses
	To increased filling (deep breath)
	To exercise
	To change of position
	To anoxemia
	To the action of nicotine
	To the action of nitroglycerine

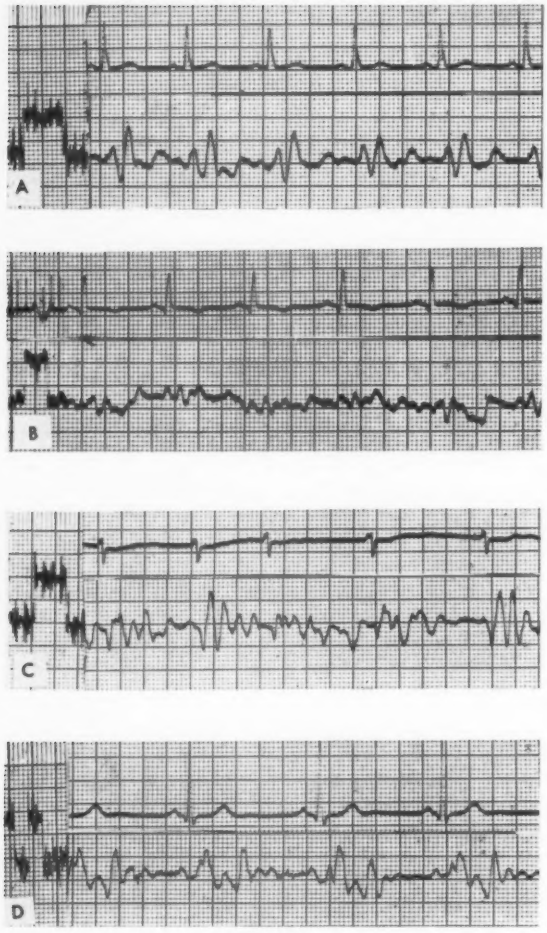

Fig. 5. Normal and abnormal high-frequency ballistocardiograms, taken simultaneously with electrocardiograms (Starr table). Ballisto calibrations are on the left. The deflection is caused by a force of 280 g while the paper runs at slow speed. (A) Normal tracing of man of 49 years. Note the ease with which the ballistic waves can be identified, the normal amplitude of H, I, and J, the short or absent K wave, the absence of resonance in diastole. This is a normal record and shows the better definition of diastolic events which has been attained by recent improvements of technic. (B) Very abnormal tracings of a 78-year-old man with generalized arteriosclerosis and old myocardial infarction. Note the extremely small amplitude of the ballistocardiogram and the distortion of the waves. Only an expert could identify the waves in the absence of a simultaneous electrocardiogram or pulse tracing. The highest wave of most systolic complexes is H. The J is very flat and usually notched. A most abnormal record indicating great cardiac weakness and a lesser degree of incoordination. (C) Abnormal tracing in 44-year-old man with rheumatic heart disease, mitral stenosis and auricular fibrillation. The ballistic complexes vary greatly from beat to beat, both in form and amplitude, the smaller being extremely small and distorted. The larger, of normal amplitude, tend to have doubled J waves. Note that the most normal and largest complexes occur after the longer diastoles; this indicates that the heart, when it is better filled, contracts more strongly. So, despite its incoordination and the weakness of some beats, this heart is still on the normal side of the Starling curve. (D) Abnormal tracings in an active overweight man, aged 64, who has no symptoms. While the amplitude is everywhere normal only the largest complexes in the respiratory cycle are normal in form. In the others the I wave either fails to reach the base line, is reduced to a notch, or is almost altogether absent. The terminal complexes (the M and N waves) are unusually large and well marked. The diminished I wave indicates that the heart is not contracting with the normal snap and the blood is not being properly accelerated at the onset of systole. The large terminal complex indicates that deceleration at the end of systole is unusually abrupt. The heart does best when, in the respiratory cycle, it is best filled, so it is on the normal side of the Starling curve. The record cannot be passed as normal but obviously the degree of abnormality is far less than in (B) and (C). If only one complex of the respiratory cycle was abnormal, I would think of the record as borderline for a man of 64, but in this record the abnormal complexes outnumber the normal.

Cardiac incoordination, indicated by abnormal record forms, is placed next in importance. Third, we have placed the detection of abnormal myocardial reactions as brought out by certain tests. This arrangement reflects our conviction that the chief value of the record lies in the identification of the physiologic state of the myocardium, thus providing physiologic information which can be added to the anatomic information which forms the basis of most cardiac diagnosis made today.

The arrangement of Table I also reflects a conviction concerning the future. The full value of ballistocardiograms in detecting cardiac function will not be secured by tests taken at rest, but by studying the heart's reaction to various kinds of stressful and beneficial situations.

Table II lists specific conditions in which we believe that information of the state of the myocardium can be used to the especial advantage of our patients. No attempt has been made to give a complete list, for one would like to have as complete information as possible about all aspects of cardiac performance in the record of every patient known to have, or suspected of having, cardiac disease. I have tried to list the items given according to my opinion of the relative value of the ballistocardiogram in such con-

ditions. Thus at the very bottom I place its value for the detection of anatomic lesions.

In this laboratory the attitude toward the information provided by the ballistocardiogram is much the same as that of every informed physician toward the blood pressure. Thus measurement of the blood pressure records a physiologic aspect of the circulation which is detected with difficulty, or not at all, by the routine physical examination and tests. Its chief value resides in the measurement itself, which contributes to our understanding of the case and is a factor in the choice of therapy. Occasionally, as in aortic regurgitation, hyperthyroidism and brain tumor, abnormalities of blood pressure may provide evidence which leads to the diagnosis of an anatomic lesion, but this is a minor aspect of its general utility.

TABLE II

Utility of the Ballistocardiogram

I	Demonstration of extent of myocardial damage or recovery
	In aging persons
	In cardiac infarction
	In angina pectoris
	In other cardiac abnormalities
II	Demonstration of the effects of therapy on myocardial function
	After digitalis
	After nitroglycerine
	After other drugs
	After operative procedures
	After abdominal support
III	Aid in making important distinctions
	In congestive failure
	Ballistocardiogram small—usual type
	Ballistocardiogram large—high output failure
	In hypertension
	Ballistocardiogram small or normal—usual type
	Ballistocardiogram large—emotion, adrenalin
IV	Aid in the detection of abnormalities of the circulation not primarily myocardial in origin
	In neurocirculatory asthenia and anxiety
	In hyper- and hypothyroidism
	In anemia
	In A. V. communications
	In increased pulmonary artery pressure
V	Aid in the detection of anatomic lesions
	Coarctation of aorta
	Aortic regurgitation
	Mitral stenosis
	Constrictive pericarditis

Let me close by stating my belief that the ballistocardiogram discloses an aspect of the heart's activity every bit as important as the blood pressure, and that, when doctors are alert to its possibilities and learn to use the information it contains, it will be just as valuable to them as is knowledge of the blood pressure today.

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Appendix

COMPARATIVE TRACINGS

NORMAL, BORDERLINE AND ABNORMAL BALLISTOCARDIOGRAMS TAKEN BY METHODS OTHER THAN THE HIGH FREQUENCY TABLE FOR COMPARISON WITH THEIR COUNTERPART IN FIGURE 5 IN THE PRECEDING ARTICLE BY DR. ISAAC STARR.

Figure 1, Courtesy of William Dock, M.D., Figure 2, Courtesy of William R. Scarborough, M.D., Figure 3, Courtesy of Ernst Jokl, M.D.

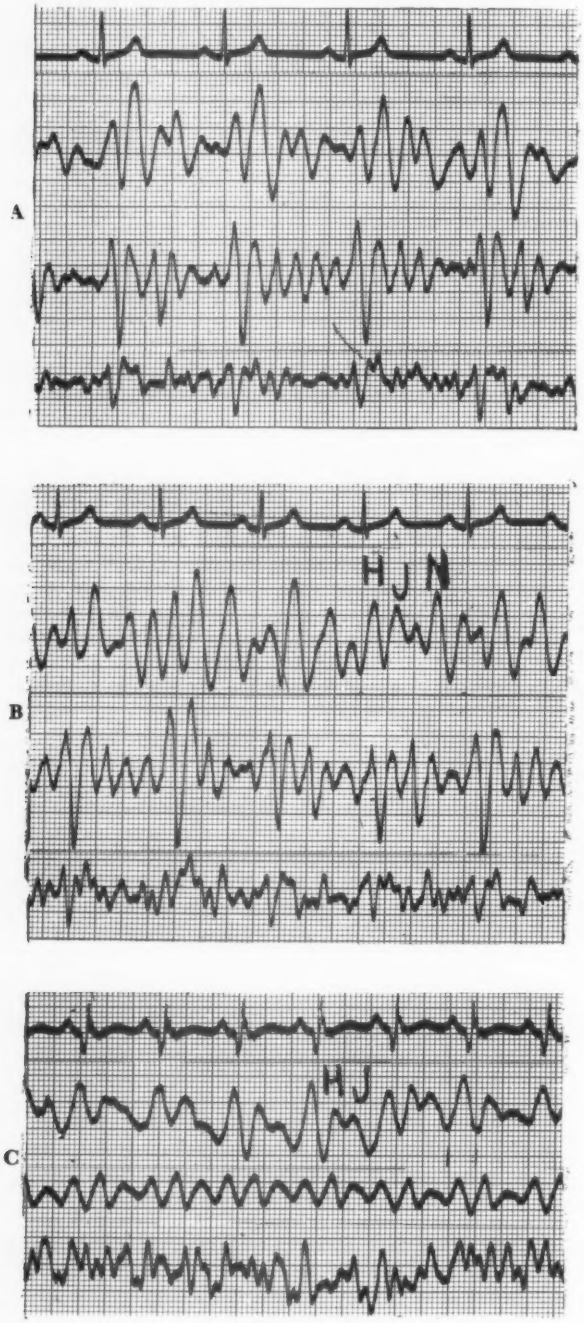


Fig. 1. Representative ballistocardiograms recorded by direct-body (shin-bar) system. (A) Normal tracings obtained from man of 57 with old healed myocardial infarction and mild anginal syndrome. Upper tracing below ECG is head-foot BCG, middle tracing is lateral BCG and lower tracing is dorsoventral BCG. On inspiration, the baseline rises on head-foot tracing; on expiration it falls. The H wave in the head-foot tracing is large but in the normal range. The L-M interval in the lateral tracing is the upper limit of normal. (B) Borderline tracings obtained from same patient after smoking cigarette. There are definitely abnormal beats during expiration with normal beats in inspiration. The systolic waves (H-I waves) decrease in the headward (top strip) and lateral (lowest strip) tracings. (C) Very abnormal tracing of 44-year-old man one year after extensive myocardial infarction. The main wave in the head-foot tracing is the presystolic wave which is larger than the systolic wave and corresponds to a loud presystolic gallop in the phonocardiogram. There is also a fused H-J wave. The lateral tracing (lower strip) shows presystolic and H waves of low amplitude but the largest in the cycle. There is a very sharp presystolic wave in the dorsoventral tracing (middle strip).

Fig. 1.

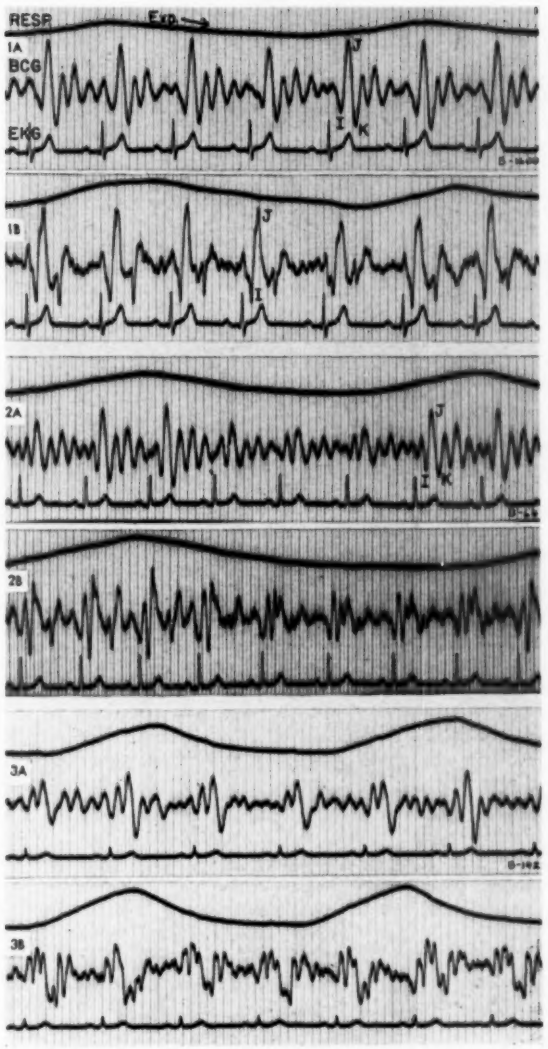
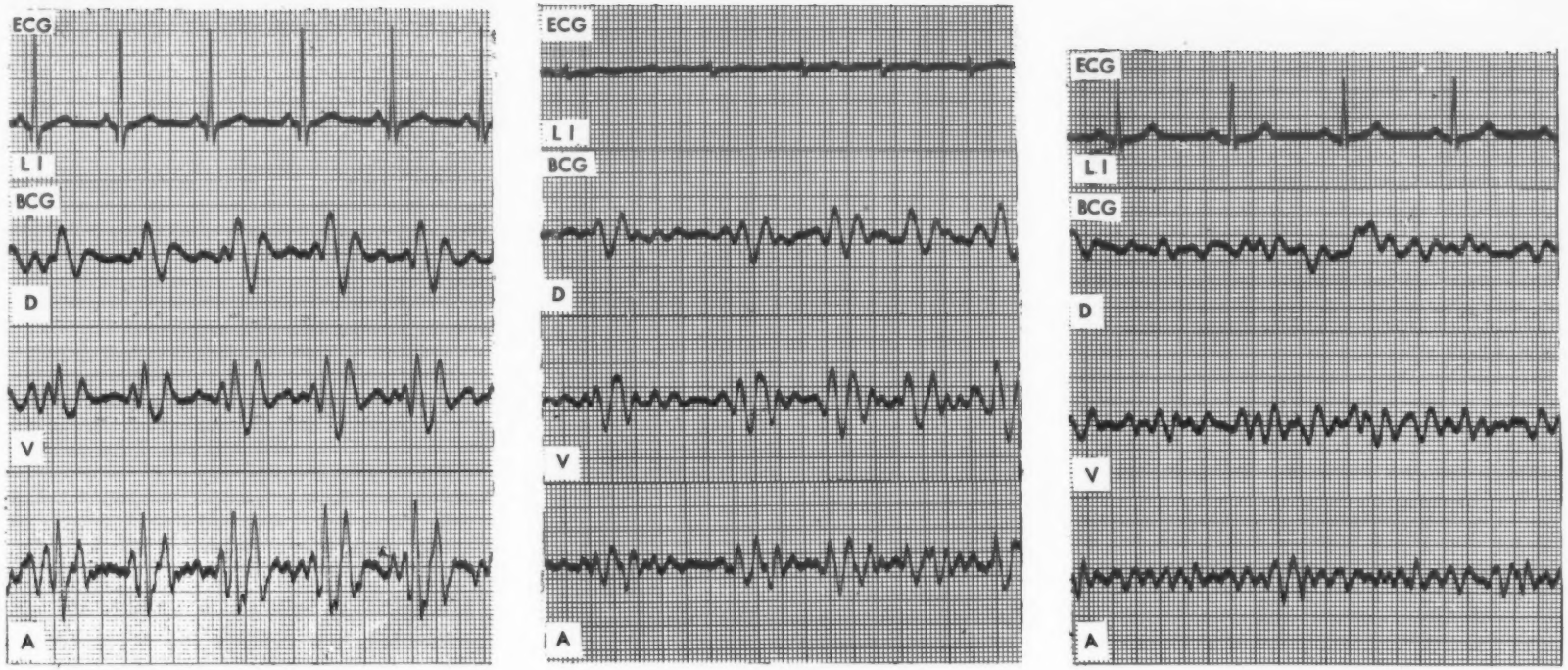


Fig. 2.

Fig. 2. Representative normal, borderline, and abnormal tracings taken with the ULF BCG. 1a, 2a, and 3a were obtained with a Starr bed while 1b, 2b, and 3b were recorded with a ULF bed on the same individual and on the same date. In each record the upper tracing (RESP) is the pneumogram (inspiration upward), the middle tracing is the BCG, and the lower tracing the ECG (L_2). Heavy time lines are 0.1 sec apart. 1a and b: From a 26-year-old normal male. The Starr record is normal. 2a and b: From a 48-year-old female. The Starr record is almost normal but is classified borderline because there is rather marked respiratory variation in amplitude and in expiratory complexes the relative amplitude of the I and J waves is small and the H waves large. In the ULF record, as in the Starr, the I and J waves are ample during inspiration but in expiratory complexes the H is tall and the J is widely doubled and low. 3a and b: From a 61-year-old male with angina pectoris. The Starr record is moderately abnormal with small or absent I waves, low J's and deep K's. The ULF record shows multiple small waves in early systole and a large footward deflection in late systole. Although there are obvious differences in the details of waveform of these Starr and ULF records, nevertheless the general pattern in the two types of records is comparable in these three subjects. This is not always the case and unexpectedly large differences in waveform of Starr and ULF ballistocardiograms from the same person are not infrequently observed. There are as yet no definite criteria of normality for ULF records.



A B C

Fig. 3. Representative tracings taken with direct body displacement, velocity, and acceleration method. (A) Normal tracing. Direct body displacement, velocity, and acceleration BCG recorded simultaneously with electrocardiogram. The complexes are all well formed, reasonably repetitive, sharp and well defined, with little body motion present during diastole. Of the three curves, the acceleration is most sharp and clear, shows the greatest amount of detail and more nearly records a greater range of the applied forces due to cardiac systole. (B) Borderline ballistocardiogram in displacement, velocity, and acceleration: The complexes are less well formed. There are marked variations not only in amplitude but also in form of the complexes with different phases of respiration; the BCG deteriorated further with exercise. (C) Abnormal tracing. No pattern is visible, even though the ECG is present to aid in identifying where the BCG complexes should be. The tracing is devoid of form, repetitiveness or, indeed, any visible ballistic complex.

Clinical Studies

Cardiac Aspects of Renal Disease*

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THE HEART and kidney are closely related in their effects on circulatory dynamics. Disorder in one organ, if progressive, invariably results in involvement of the other. In considering renal disorders that affect the heart, one must consider two possibilities: (1) whether cardiac manifestations are the result of altered renal physiology or (2) whether both organs are primarily involved in the same basic pathologic process.

The latter group includes a variety of diseases. These may be categorized as collagen disease, systemic vascular disease, infectious or neoplastic disease, and disease due to toxic agents. Among the collagen diseases which include lupus erythematosus disseminata, polyarteritis nodosa, rheumatic arteritis and scleroderma, the basic pathology may be similar and both the heart and kidneys are affected.[1] Systemic vascular diseases include hypertensive cardiovascular disease, generalized arteriolar sclerosis and toxemia of pregnancy.[2,3] Diphtheria and scarlet fever may cause myocarditis and nephritis. Tertiary lues may rarely result in a nephrotic syndrome as well as in aortitis. Neoplastic processes such as lymphomas may involve both organs. Toxic agents, notably heavy metals and carbon tetrachloride, may damage both the heart and kidney, although the latter agent is clinically more nephrotoxic than cardiotoxic.

Glomerulonephritis, amyloid disease and epidemic hemorrhagic fever may not fall into any of the above categories. In the latter two there is definite evidence that both heart and kidney are primarily effected. This may not be true in acute glomerulonephritis. In support of the contention that the heart is primarily involved in acute glomerulonephritis, it has been observed that clinical signs of cardiac insufficiency and electrocardiographic abnormalities may precede edema and urinopathy.[4,5] Pathologically, Aschoff cells, interstitial serous effusion in the myocardium,[6] and cardiac enlargement without preceding hypertension[7] have been described. On the other hand, it has been observed that the cardiac output may be normal in the presence of symptoms commonly attributed to congestive heart failure. This is felt by some to be incompatible with the diagnosis of myocarditis.[8,9] Certainly the pathogenesis of the apparent heart failure in acute glomerulonephritis is poorly understood, and its clarification must await further study.[10] Clinically, the renal element usually predominates in the initial stages of the disease.

CARDIAC MANIFESTATIONS OF ALTERED RENAL PHYSIOLOGY

Most commonly, cardiac manifestations of kidney disease arise as a result of alterations in renal physiology and do not involve the myocardium primarily. The principles of management, however, are similar in both instances. The fluid and electrolyte abnormalities seen in acute and chronic renal disease and their resultant cardiac effects constitute the major hazard to the patient.

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TABLE I

Table Showing the Daily Changes in Patient D. F. with Chronic Glomerulonephritis (Case 1)

DATE	WEIGHT Kgm	INTAKE cc	URINE OUTPUT cc	PLASMA SODIUM mEq/L	BUN mgm%
8/2	89.0	2000	750	138	100
3	88.6	3740	1275		
4	90.0	2600	1000		101
5	91.0	3540	1300	130	93
6	91.0	4150	1500		
7	92.0	3335	1375	125	82
8	94.4	3450	1000		
9	96.3	3350	1300		79
10	97.6	1500	1000	107	78
11	PULMONARY EDEMA				

ALTERED FLUID BALANCE

In acute renal failure, overhydration may lead to congestive heart failure and pulmonary edema. It is generally recognized that fluid replacement should be limited to matching urine output, inordinate loss from other sites (vomiting and diarrhea), and insensible loss. In our own experience, the insensible loss should be estimated at 600–800 ml a day. Daily weights provide the best index of the state of hydration. Under optimal conditions the patient will lose from $^1/_4$ to $^1/_2$ kg a day because of the associated caloric deficit. A patient maintained at constant weight *may* be overhydrated. After 10 days, such a patient will have accumulated $2^1/_2$ to 5 *l* of fluid, and pulmonary edema may ensue.

In chronic renal disease overhydration may also occur in spite of an adequate urine output. Attempts to "wash out the BUN," though frequently producing a higher urinary output, may result in overhydration. In advanced stages of renal disease, patients who are unable to tolerate a salt load often have the same difficulty with water. Optimal fluid management for such a patient should include sufficient fluid to maintain the maximum urine output obtainable *without weight gain*. Otherwise hypervolemia leading to heart failure or pulmonary edema may result. The following case illustrates this:

Case 1. D. F., a 52-year-old woman with chronic glomerulonephritis, was admitted to another hospital in

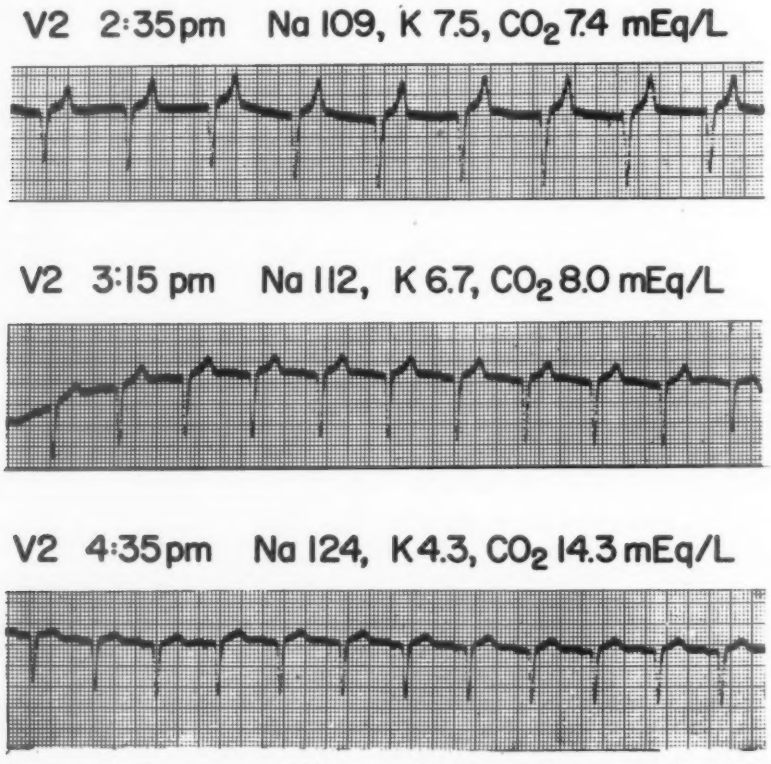

Fig. 1. Case 2. Acute renal failure. Serial electrocardiograms during which hyperpotassemia was corrected by hemodialysis.

congestive heart failure. After administration of digitalis she improved. The BUN at this time was 100 mg %. In an attempt to "wash out the BUN," 2 to 4 *l* of fluid were administered daily (Table I). The result was an 8.6 kg weight gain despite a urine output of 750 to 1,500 ml a day. The fall in BUN to 78 and the fall in plasma sodium from 138 to 107 meq/*l* clearly represented dilution. Symptoms of congestive heart failure recurred on the ninth day and terminated in pulmonary edema despite a belated attempt to restrict fluids.

ALTERED ELECTROLYTE BALANCE

Hyperpotassemia: Electrolyte alterations occur in both acute and chronic renal disease. The electrocardiogram is the most reliable clinical guide to cardiotoxicity.[11] The most serious electrolyte derangement in terms of cardiac effect is hyperpotassemia. Intraventricular heart block and atrial and ventricular arrhythmias can result.

CASE 2. J. H., a 53-year-old woman with acute renal failure, was admitted in a moribund condition. Her electrocardiogram revealed peaked T waves, slight prolongation of the QRS complex, and atrial arrest (Fig. 1, 2:35 p.m.). The plasma potassium was 7.5 meq/*l*, sodium 109 meq/*l*, and the CO_2 7.4 mM/*l*. Dialysis with the artificial kidney corrected the plasma electrolyte abnormalities, and this was associated with reversion of the electrocardiographic alterations to normal (Fig. 1, 4:35 p.m.).

Electrocardiographic correlation with specific plasma electrolyte levels is poor[11,12] probably reflecting the contribution of other ions and intra-extracellular relationships.[13,14] Clinically, hyponatremia and acidosis enhance the effects of hyperpotassemia as demonstrated by the following case report.

CASE 3. H. M., a 28-year-old woman with acute renal failure, was transferred to Bellevue Hospital for dialysis with the artificial kidney. On admission, the plasma potassium was 8.6 meq/*l*, the CO_2 combining power 1.3 mM/*l*, and the blood pH 7.10. The electrocardiogram showed atrial arrest and marked intraventricular heart block (Fig. 2, 5:00 p.m.). Intravenous 5 per cent sodium bicarbonate was begun at once, while the artificial kidney was being prepared. At the start of hemodialysis, two hours later, 12 g of sodium bicarbonate had been administered and the electrocardiogram showed restoration of normal sinus rhythm and reduction of the intraventricular heart block (Fig. 2, 7:15 p.m.). At this time the plasma potassium had dropped to 6.5 meq/*l*, and the pH was 7.32. The disproportionate lag in correction of the carbon dioxide combining power is a phenomenon we have observed in other patients and probably reflects respiratory compensation.

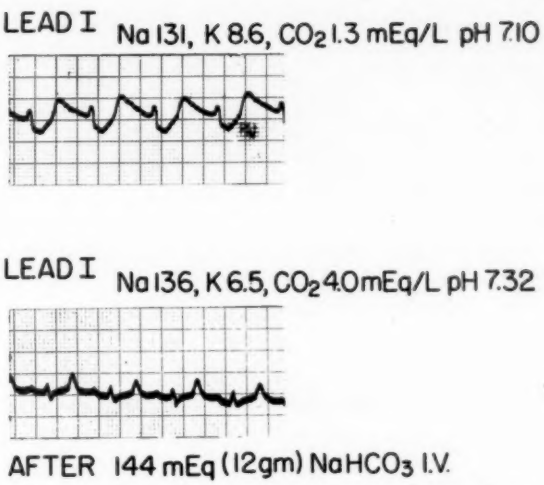

Fig. 2. Case 3. Acute renal failure. Electrocardiograms before and after correction of hyperpotassemia and acidosis by infusion of sodium bicarbonate.

In the diuretic phase of acute renal failure and in chronic renal disease, urinary electrolyte concentration may be fixed for long periods. Hyperpotassemia may continue to be a problem even in the face of adequate urinary volumes. This is not generally appreciated. In such situations, potassium balance may be altered by manipulating intake. This is well illustrated in the following case report.

CASE 4. C. O., a 10-year-old girl with subacute glomerulonephritis, was initially oliguric. As urine output increased to a liter a day the patient was changed to an unrestricted potassium intake. The urinary potassium concentration remained fixed at about 25.0 meq/*l* and daily intake exceeded excretion (Table II). The

TABLE II

Table Showing the Daily Changes in Patient C. O. with Subacute Glomerulonephritis (Case 4)

DATE	DIET	PLASMA POTASSIUM mEq/L	URINE POTASSIUM mEq/L	INTAKE cc	URINE OUTPUT cc	WEIGHT Kgm
9/12	↑ ad lib	3.9	22.3	2300	2100	32.3
13	potassium			2420	1790	
14	intake	4.9	23.0	1850	1880	33.6
15				1920	1340	33.5
16		6.3	26.0	1920	1335	
17				1530	discarded	32.8
18		6.5	30.9	1140	705	33.8
19	↓	7.1	25.0	1400	1040	
20	↑	6.3	21.5	1320	950	
21	potassium	6.0	22.5	1405	1060	35.2
22	free		19.1	1210	1025	35.7
23	diet	5.2	17.9	1500	935	34.5
24	↓	4.3	23.6	1540	950	35.9

plasma potassium rose to 7.1 meq/*l*. When potassium restriction was reinstituted the plasma potassium returned to normal.

Since fixation of renal electrolyte excretion may occur at varying levels in different patients, determination of the urinary electrolyte concentrations will provide an accurate guide to replacement in the diuretic phase of acute renal failure and in chronic renal disease.

The treatment of hyperpotassemia should include restriction of potassium intake and correction of hyponatremia and acidosis if present. Infusions of glucose and insulin and administration of cation exchange resins may be of temporary benefit. Since tissue catabolism results in release of potassium, effort should be made to maintain caloric balance. Testosterone may reduce tissue breakdown through its anabolic effects,[11] but this measure has not been necessary in our hands. Hemodialysis with the artificial kidney is a useful adjunct to these measures.

Other Electrolyte Disturbances: Other electrolyte abnormalities are frequently seen in the symptomatic uremic patient. Mild degrees of hyponatremia and acidosis need not be corrected although maintenance to prevent further decreases in their concentration is advisable. It should be remembered that sudden elevation of blood pH will decrease ionized calcium and may result in tetany. Therefore, it is advisable to administer calcium if acidosis is to be corrected. Hypopotassemia has been shown to be associated with renal damage and dysfunction[15] and should be corrected promptly.

Digitalis Toxicity and Electrolyte Changes: Since congestive heart failure is a frequent complication in the uremic state, many patients will have received digitalis. This is clinically significant because rapid correction of hyperpotassemia may produce signs of digitalis toxicity. The following case report demonstrates this point.

Case 5. E. K., a 16-year-old female with chronic pyelonephritis, was dialyzed because of severe uremic symptoms and a plasma potassium elevation to 7.4 meq/*l*. The rhythm was normal sinus (Fig. 3, 4:15 p.m.). She had received digitalis because of congestive heart failure. During dialysis, the potassium fell to 4.7 meq/*l* and the electrocardiogram at that time showed runs of nodal rhythm (Fig. 3, 6:00 p.m.). With addition of potassium to the rinsing bath the rhythm promptly changed to normal sinus, initially with 1st degree heart block (Fig. 3, 7:15 p.m.). The disappearance of the signs of digitalis toxicity is probably related to change in intra-extracellular ion relationship, since the final plasma potassium (7:45 p.m.) had not significantly changed from the time of toxicity.

Since calcium and potassium ions are antagonistic in their cardiac effects, correction of

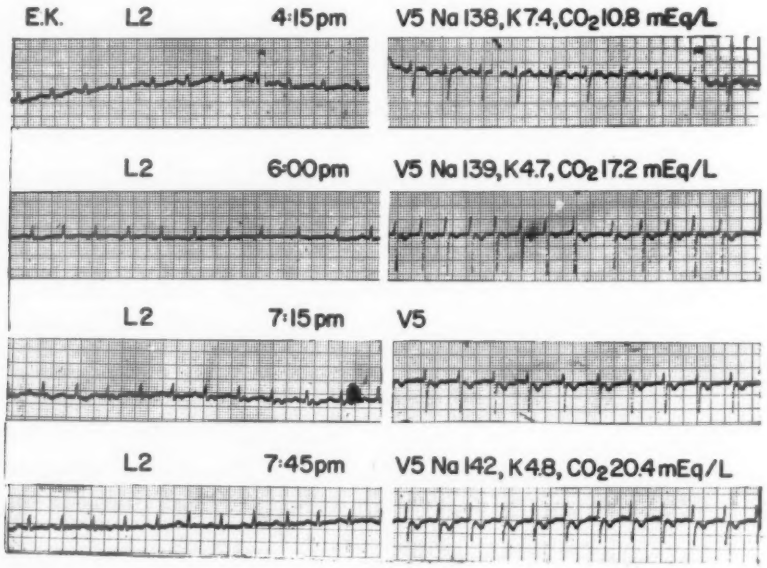

Fig. 3. Case 5. Severe uremia. Series of electrocardiograms during hemodialysis demonstrating the relationship between potassium, acidosis, and digitalis toxicity.

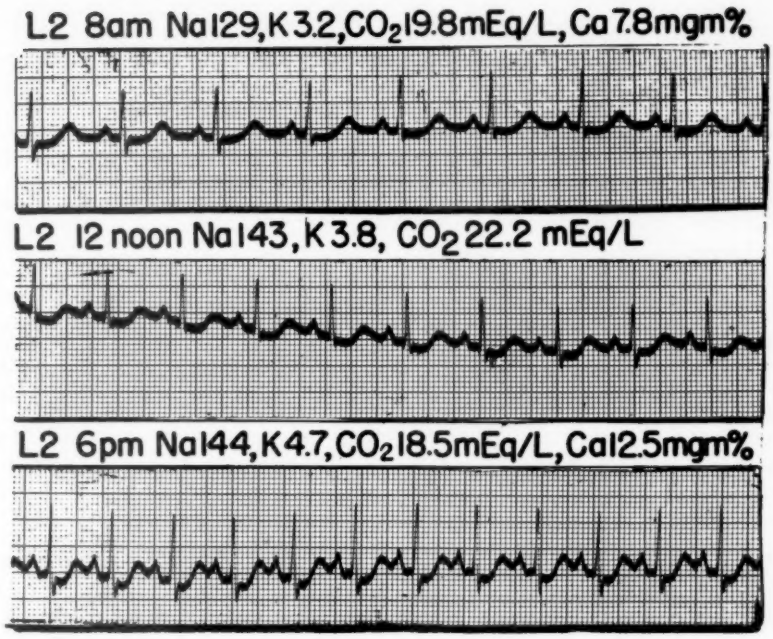

Fig. 4. Case 6. Chronic uremia. Series of electrocardiograms illustrating the emergence of "digitalis effect" with correction of hypocalcemia during hemodialysis.

hypocalcemia may result in similar alterations. The following patient had the appearance of "digitalis effect" on electrocardiogram during dialysis.

CASE 6. P. D., a 42-year-old male with chronic uremia due to polycystic disease, was dialyzed because of severe uremic symptoms. His serum calcium was 7.8 mg % (Fig. 4, 8:00 a.m.). He had received digitalis. During dialysis the calcium rose to 12.5 mg % and electrocardiographic evidence of "digitalis effect" appeared (Fig. 4, 6:00 p.m.).

OTHER CARDIAC EFFECTS OF UREMIA

Other complications of the uremic syndrome may have cardiac manifestations. Hypertension may result in left ventricular hypertrophy and dilatation leading to congestive heart failure. It has already been mentioned that the symptoms of congestive heart failure may appear in acute glomerulonephritis without hypertension. Uremic pericarditis occurs more frequently in chronic than acute renal disease and in the former is of graver prognostic significance.[16] In either, it may undergo exacerbation and remission.[17] Cardiac tamponade is infrequently seen in its presence.[18] Anemia also occurs in uremia, and may contribute to the development of congestive heart failure.[19] Transfusions, therefore, often become an essential part of management. Acute increase of the circulating blood volume constitutes a potential hazard to these patients with already decreased cardiac reserve. Packed red blood cells infused slowly through a three-way stopcock which allows frequent determination of the venous pressure during transfusion will minimize this danger.

SUMMARY

The heart and the kidney are interdependent in the maintenance of circulatory homeostasis. It is not surprising, therefore, that cardiac manifestations are frequently seen in the course of renal disease.

Cardiac abnormalities may occur concomitant with renal disease if both share the same basic pathologic process. Cardiac manifestations may also appear as a result of abnormalities in renal function leading to altered fluid and electrolyte balance. In advanced stages of the uremic syndrome anatomic changes in the heart often result. The pathogenesis of many cardiac manifestations in uremia, however, remains obscure.

Management of the renal disease is similar in all these processes. The principles as outlined may be applied with minimum laboratory facilities. In maintenance of fluid balance, total daily intake should match total daily loss. Daily measurement of intake and output supplemented by determinations of body weight are readily available, valuable clinical guides.

Electrolyte management also involves replacement of specific losses. In complex situations, determination of urinary as well as plasma electrolyte concentrations may prove helpful in calculation of daily needs. Electrolyte abnormalities are most serious in their cardiac effects. The resultant electrocardiographic changes represent the sum total of a complex ion relationship. With changing electrolyte patterns, therefore, frequent electrocardiographic observations are necessary. Specific abnormalities are discussed and illustrated with case examples.

The dangers of electrolyte abnormalities and overhydration in the oliguric patient and the basic principles of their management are well recognized. The same principles applied in all phases of renal disease can result in gratifying improvement in useful life expectancy.

Acknowledgments

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Pheochromocytoma

Experiences in the Diagnosis and Treatment*

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ALTHOUGH Frankel[1] published the first report describing pheochromocytoma as early as 1896, the tumors arising in the adrenal gland or in other chromaffin tissue were not given the attention they deserved until advances in diagnosis and surgery led to the discovery of an increasing number of cases. The importance of such tumors became obvious when Smithwick[2] reported 5 cases of pheochromocytoma among the 1,000 patients sympathectomized because of hypertension and when Green[3] stated that pheochromocytoma might cause persistent (and not only paroxysmal, as earlier believed) hypertension in about 70 per cent of cases.

The tumor endangers the life of the patient harboring it for two reasons: (1) The episodes of paroxysmal hypertension may lead to acute left heart failure with pulmonary edema, ventricular fibrillation, and later to cerebral hemorrhage; and (2) Prolonged hypertension which may simulate either benign or malignant hypertensive disease clinically will shorten the life expectancy of the patient.

PATHOPHYSIOLOGY

The pathophysiology of the disease caused by pheochromocytoma was not fully elucidated until Von Euler[4] and Holton[5] reported that the tumor contained epinephrine and norepinephrine, and secreted these hormones in paroxysms or continuously. These "catecholamines" or "pressor amines" produce pharmacologic effects which manifest themselves in what is known to be the clinical picture of pheochromocytoma. Epinephrine increases the heart rate, producing thereby a minute volume hypertension, decreases peripheral vascular resistance and gives rise to stenocardiac complaints by causing a relative impairment of coronary flow. It elevates the blood sugar level and raises the basal metabolic rate. Wada[6] has shown recently that sympathetic excitation produces increased sweating too.

In the hypertension induced by norepinephrine, the peripheral vascular resistance is increased, but neither the blood sugar, nor the heart rate, nor the basal metabolic rate are affected. It is important to emphasize these physiologic differences because the tumor is known to produce first this, then the other catecholamine, in variable proportions. Thus, for example, when norepinephrine is being produced in excess by the tumor, the clinical picture will not necessarily include hyperglycemia, glycosuria, or an elevated basal metabolism.

CLINICAL DIAGNOSIS

During the past decade a number of clinical tests have been developed for the diagnosis of pheochromocytoma. These are useful since paroxysmal hypertension may be due not only to pheochromocytoma, but also to psychic stress, ependymoma occluding the third cerebral ventricle like a ball, diencephalic epilepsy caused by hypothalamic tumor and argentaffinoma (Snow *et al.*).[7] The presence of pheochromocytoma should be suspected if the patient with hypertension exhibits excessive

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sweating, vasomotor disturbance, increased metabolism, orthostatic hypotension, as well as tachycardia and hyperglycemia. Nonetheless, it should be borne in mind that, although infrequently, the clinical picture of pheochromocytoma may so closely resemble that of hypertensive vascular disease that the true cause of the complaints will be elucidated only when the adrenals are explored during a thoracolumbar sympathectomy.

Provocative Tests: In the presence of pheochromocytoma, attacks may be provoked by change in posture, emotional stress, physical effort, hyperventilation, cold, abdominal massage, but often the provocative factor may escape detection. At present the most widely used method for provoking an attack in the patient suspected of having pheochromocytoma is the histamine test described by Roth and Kvale.[8] This test, however, may be just as dangerous as any other measure of provocation and for this reason should be used with great caution.

Blood Pressure Lowering Tests: The other methods of diagnosis include the use of drugs to lower the blood pressure, such as Benodaine®, Dibenamine® and Regitine®. These are less dangerous, but also less reliable. They act on the neuromuscular junction, presumably competing with the catechol amines, preventing the latter from reaching their site of action and thereby lower blood pressure, or sometimes cause collapse. These agents are ganglion-blocking ones only at concentrations greater than used in the test. As these methods yield results difficult to evaluate, and may give rise to untoward complications, (Goldenberg *et al.*)[13] we prefer the most reliable method available at present, namely, the estimation of catecholamine in the urine or blood.

Urinary Excretion of Catecholamines: This test is based on the observation that on the days the patient has an attack or if he has a persistent hypertension, the urine contains more than 70 to 80 μg of catecholamine per 24 hours. Levels may rise to several hundred or 1,000 μg. In general, the catecholamine output is not increased in hypertensive disease, although according to a recent report by Von Euler[9] moderately increased output may occur in such cases too. When the output is markedly increased, the diagnosis of pheochromocytoma is almost unquestionable. For this reason the estimation of catecholamine will supply differential diagnostic evidence in cases of paroxysmal hypertension on one hand and cases of hypertensive vascular disease on the other. The test will distinguish with a high degree of certainty the hypertension due to pheochromocytoma.

We have been using the quantitative urinary catecholamine test at the University of Budapest, Department of Medicine, for three years now and this test has proved to be a valuable aid in the diagnosis of pheochromocytoma. For this reason we feel justified to give an account of the observations made, both with the aluminum hydroxide absorption method of Von Euler[11] and with the fast biologic assay technic of Moulton and Willoughby,[12] involving the use of untreated urine, assayed in the cat.

Localization of Tumor: After the diagnosis of pheochromocytoma is established on the basis of clinical and laboratory evidence, the exact localization of the tumor prior to surgery still remains a problem. The tumor occurs more often in the right than in the left adrenal, and is bilateral in a small percentage of cases. It may arise also in the peri-aortic paraganglia. Von Euler[4] has suggested that the output of epinephrine as related to that of norepinephrine might be relied upon in determining whether the tumor was one of common location or ectopic. In some cases plain films of the abdomen, pyelography, tomography, perirenal air injection or retroperitoneal pneumograms will help to locate the tumor. The latter two procedures are not without risk because they may elicit a prolonged attack by causing compression of the neoplasm.

Surgical Treatment

In the majority of cases, surgical removal of the tumor results in final recovery unless irreversible vascular lesions are already present. The recently introduced conservative measures such as x-ray irradiation, prolonged Thiouracil and Regitine administration have not fulfilled the hopes attached to them (Kleinsorge *et al.*).[10]

Precautions During Surgery: Surgery is not without hazards, the mortality of the operation

being still as high as 20 per cent. An attack may be provoked by the inhalation anesthesia itself or by the handling of the tumor during operation. For this reason care should be taken not to touch the tumor during removal and after it has been isolated. Its hilus and the vessels running to it should be clamped at the same time and the tumor should be excised in this way. A lethal shock may often develop after the tumor is removed. The development of an attack during operation can be prevented by the use of a neuromuscular blocking agent. However, it should be borne in mind that after the use of the latter, the common pressor agents will fail to relieve postoperative shock. In such cases Pitressin® which acts directly on the blood vessels may prove to be effective, but it impairs coronary circulation.

Among the surgical approaches recommended, transthoracic, transdiaphragmatic, high lumbar and transabdominal, the transabdominal seems to be the one to be preferred, as it permits careful examination of both adrenals and the periaortic region.

Preoperative Preparation of Patient: Induction of anesthesia is begun in the ward, by injecting pentothal intravenously. Whole blood for transfusion as well as 5 mg norepinephrine dissolved in 500 ml 5 per cent dextrose is held in readiness, the latter to be used intravenously to prevent drops in blood pressure if the necessity arises. In one case, an acute elevation of blood pressure could be successfully relieved by the intravenous administration of 1 cc Hydergine, which is a mixture of dihydroergocornine, dihydroergocristine and dihydroergokryptine in equal proportions. Hydergine has a marked central as well as a peripheral action and has been shown to have hypotensive effect without causing collapse in hypertensives (Barcroft, Konzett and Swan).[14] Wilkins *et al.*[15] reported their findings of a patient with pheochromocytoma before and after successful operation. Dihydroergokryptine, one of the hydrogenated ergot alkaloids, was used in a dose of 0.5 mg intravenously resulting in a prompt relief of symptoms, concomitant with a rapid reduction of greatly elevated blood pressure. It is interesting to note that Mandl[16] could produce a hypotensive effect with 1 cc of Hydergine intravenously when hypertension occurred in a histamine test.

When the exact site of the tumor was not known, the right transabdominal approach was employed because the incision made transversally along the right costal arc could be readily extended to the left side if so required. In this way not only the left adrenal, but also the whole abdomen could be examined.

Case Histories

Case 1. O. A., male, age 54 years, had complaints of one year's duration. These included intense palpitation on exercise or emotional stress or even during sleep, accompanied by throbbing headache in the temporal region, thoracic distress, trembling, pallor, nausea, vomiting. The attacks recurred more and more often. While at our department, crises occurred daily, but there were days during which 10 to 15 attacks developed. During an attack systolic blood pressure rose to as high as 280 mm Hg or was over 300, the diastolic pressure varying in the range of 180 to 210 mm Hg. When it ceased spontaneously in a few minutes the attack was usually followed by a grave collapse which ended only after a second attack developed on many an occasion. There were days during which the blood pressure oscillated 10 to 15 times between the maximal upper and measurable lower limits. During the interval between attacks the blood pressure was 130/90.

Pallid face and a moderate enlargement of the heart to the left were the only pathologic changes detectable at physical examination. The blood sugar level during attack was 180 mg per cent, whereas in the interval between bouts it was 100 mg per cent.

A plain x-ray film of the abdomen and intravenous pyelogram revealed no abnormality except for a calculus in the right kidney pelvis. Depending on the duration of the attack and collapse, respectively, NPN varied from 33 to 76 mg per cent. At the same time the endogenous creatinine clearance test showed values varying from 61 to 31 ml. Examination of the ocular fundi showed narrowed arteries. The ECG changes included flattened T waves, a P-Q interval prolonged to 0.40 sec after an attack and occasional Wenkebach periods due to A-V block. As the patient was in a very poor condition, perirenal or retroperitoneal air injection was not carried out. In a 24-hour period during which 10 attacks occurred, the urinary catecholamine output was as high as 1,000 μg.

At operation, employing the right transabdominal approach, the tumor was found in the right adrenal. On touching the tumor the blood pressure jumped to 240/140 but could be depressed to around 180 systolic by the intravenous administration of 0.66 mg Hydergine. On clamping the stem of the tumor the blood pressure dropped to an unmeasurable level within a few seconds. Norepinephrine infusion was started without

delay. The blood pressure rose to 130/90 and could be maintained at that level by adequately adjusting the drip rate. It is interesting that even as late as 24 hours after operation, interruption of the infusion for a few seconds when the flasks were exchanged sufficed to drop the blood pressure to unmeasurable levels. Norepinephrine infusion was continued for 50 hours during which time the blood pressure was determined every 10 minutes. After that period the blood pressure remained at the 130/90 level. The total amount of norepinephrine infused was as high as 63 mg.

The excised tumor weighed 44 g and proved histologically to be a typical pheochromocytoma. It contained 3,200 μg total catecholamine per gram tumor tissue, of which 80 per cent was epinephrine and 20 per cent norepinephrine. On the day of norepinephrine infusion the urinary output was 106 μg as compared to the 30 μg value obtained after infusion was discontinued.

The patient made an uneventful recovery. At a follow-up examination made six months after operation he felt well, had no seizure, and his blood pressure was firmly established at 150/90.

Case 2. H. B., male, age six years was admitted for hypertension. In the past he had had measles and was admitted to a hospital for infectious diseases where he bit the thermometer and swallowed the mercury in it. For this reason his subsequent complaints were ascribed by some of the doctors who saw him to mercury poisoning. Two years prior to admission to our department the boy developed attacks involving extreme blanching, elevation of blood pressure and acceleration of pulse. On admission he was found to be underdeveloped, seeming to be about two years younger than he actually was. In general, his blood pressure was around 200/140 mm Hg, but he had many attacks a day, during which the blood pressure rose to higher levels. Excessive sweating and almost imperceptible pulse were prominent symptoms during these attacks. The blood sugar level was not elevated during an attack. Basal metabolic rate was not determined. Eye examination revealed papilledema and striae of hemorrhage in the ocular fundi.

Laboratory findings included creatinine clearance of 15 ml./min, isosthenuria with compensatory polyuria, normal NPN level and a catecholamine output of 1,600 and 2,000 μg, respectively, during a 48-hour period.

Renal function being severely impaired, surgery was not contemplated. The patient developed convulsive seizures which could be relieved by the intravenous administration of sodium amytal. For further treatment the patient was transferred to the Department of Pediatrics where he died from cerebral hemorrage. At autopsy two small nut-sized, typical pheochromocytomas were found, one on the superior pole of each adrenal.

Case 3. P. S., male, age 26 years, was operated on two years before admission because of pheochromocytoma. After having no complaints for one month after operation, his attacks recurred. The attacks which were provoked by exertion or emotion, but which also occurred during sleep, were characterized by blanching and sweating without tachycardia. In spite of the absence of the latter, he complained of throbbing headache and palpitation. Physical examination revealed no pathology. Urinalysis showed a specific gravity of 1.015 and no pathologic changes. The blood pressure was 125/90 and during an attack rose to 210/110. Blood sugar was not tested during an attack. In the interval between attacks it was 93 mg per cent. Urinary catecholamine output was 196 and 300 μg respectively, in 24 hours. Retroperitoneal air injection revealed an elongation of the superior pole of the left kidney. Histamine base (0.05 mg intravenously) provoked a severe crisis.

Operation was performed through a transabdominal incision. No pathology was detectable at the site of the previous operation on the right side. On the left side medial to the superior pole of the kidney, alongside the aorta, a cherry-sized tumor, and in the adrenal a somewhat larger tumor, were found and removed. The histologically typical pheochromocytoma contained 1,000 μg total catecholamine per gram tumor tissue. No untoward complications occurred either during surgery or postoperatively.

Case 4. R. A., female, age 19 years, was admitted because she was suspected of having pheochromocytoma, after having been treated for carditis and hyperthyroidism, respectively, for three years. On admission she was found to be underdeveloped and extremely pale. Physical examination revealed no pathology except for the moderate enlargement of the heart toward the left side. Blood pressure was persistently at a level of 240/160. While under our observation no attacks occurred. The pulse rate varied from 120 to 140 per min and could not be influenced either by digitalis or by thiouracil or by sedative therapy. Basal metabolic rate was increased by 50 to 60 per cent. Repeated creatinine clearance tests yielded values varying from 96 to 140 ml. At the same time the specific gravity of urine did not exceed 1.010. Repeated tests showed normal blood sugar values. Urinalysis revealed 2 per cent albumin.

In view of the extreme tachycardia and the hypertension which appeared to be clinically of the malignant type, the histamine test was not carried out. The regitine test was positive, as the initial blood pressure of 200/150 sank to 120/70. The eye grounds showed extensive hemorrhage and degeneration as well as a pattern suggesting malignant hypertension. Retroperitoneal pneumograms revealed the presence of a cap-like tumor on the left adrenal. Twenty-four hour urine was tested repeatedly for catecholamine, and the results obtained were 500, 300 and 245 μg, respectively.

At operation by transabdominal approach, a walnut and a cherry sized tumor were removed from the right adrenal. Another chestnut sized growth was found at the level of the right superior adrenal pole, extending below the vena cava. This too was excised. During operation the clamping of the stem of the tumor caused the blood pressure to drop below measurable level. Norepinephrine infusion was started and the blood

pressure returned to normal. However, on exploring the left adrenal another fall of blood pressure took place. This time norepinephrine proved to be ineffective and the patient died of shock. The histological diagnosis was pheochromocytoma of the right adrenal. The tumors excised contained 600 μg total catecholamine per g tumor tissue. The growth removed from the left side proved to be nontypical aberrant splenic tissue.

The following 3 cases were of outstanding interest because pheochromocytoma was suspected from the presence of paroxysmal hypertension and other clinical symptoms, but in which repeated estimations showed the urinary output of catecholamines to be normal. In these cases the attacks discontinued on sedation.

Case 5. L. I., age 19 years, female, suffered an electric shock trauma on the skull in 1950 and lost consciousness for awhile. Soon after that episode she developed frequent attacks characterized by hypertension, tachycardia, profuse sweating, increased gastrointestinal activity and intense headache. The attacks recurred six to eight times a day and lasted for a few minutes to hours. However, there was a period several months in duration without a single attack. Pheochromocytoma was suspected and the patient was admitted to the Department of Medicine.

Blood sugar level was not elevated during an attack. The histamine test failed to provoke a crisis on three occasions. Regitine (5 mg intravenously) had no influence on the attack. The attack which could not be provoked with cold water or massage either, ceased instantly on the intravenous injection of 0.5 g sodium amytal. Retroperitoneal air injection showed normal relations. Urinary catecholamine was estimated four times and was found never to exceed 50 μg in 24 hours.

On this basis the diagnosis of pheochromocytoma was rejected and the patient was transferred to the department of neurology and psychiatry where a detailed analysis of the attacks showed them to be due to hypothalamic pathology. The overlapping though fragmented occurrence of sympathetic and parasympathetic stimuli during an attack, fit into the pattern of diencephalic autonomic epilepsy described several times by Penfield. Central sympathico- and parasympathicolytic agents brought some relief, but the attacks continued in a rudimentary form until chlorpromazine hydrochloride (largactil), which acts on the vegetative centers in the diencephalon, was administered. Intravenous chlorpromazine relieved the attack in a few minutes, whereas chronic treatment with tablets reduced the frequency and intensity of bouts, so that the patient had almost no complaints.

Case 6. V. L., female, age 52 years, had been having recurrent attacks of elevation of blood pressure up to 220/150 since menopausal age. During an attack she blanched, did not sweat, and the blood pressure rose to 300/202. Blood sugar was 228 and 344 mg per cent, respectively. In the interval between attacks the blood sugar was at normal levels. Basal metabolism showed a 40 per cent increase. Retroperitoneal air injection detected no tumor. Regitine 5 mg intravenously did not diminish the blood pressure. Urinary catecholamine was 32 and 44 μg, respectively, in 24 hours. Although the clinical picture strongly suggested pheochromocytoma, this diagnosis was rejected in view of the low pressor amine level in the urine. Rhodanate,* reserpine, and sedative therapy resulted in freedom from attacks and complaints.

Case 7. Mrs. J. J., age 44 years, was admitted because of hypertension and cardiac distress of six months' duration, during which period she lost consciousness on two occasions. Pheochromocytoma was suspected. The basal metabolic rate was plus 24 per cent, blood sugar was 138 mg per cent, and catecholamine in the urine was 15 μg in 24 hours. The complaints were then suspected to be neurogenic in origin. Combined rhodan and reserpine therapy resulted in full recovery.

Discussion

Cases 1 and 3, were ones showing the typical clinical symptoms of pheochromocytoma, whereas cases 2 and 4 might have been misdiagnosed if the urinary catecholamine had not been estimated. In case 1, in which hypertension was paroxysmal as well as in case 4, in which it was continuous, excessive doses of norepinephrine had to be infused during and after operation. This fact proves beyond doubt that in these patients the prolonged norepinephrinemia resulted in a decreased sensitivity of sympathetic nerve endings or in an increased tolerance to norepinephrine. The elevation of blood pressure during operation could be counteracted by Hydergine administration (case 1).

It is worthwhile to deal in some detail with case 2, that of a boy six years old. In this case the clinical picture suggested malignant hypertension. Although earlier studies made because of hypertension did not exclude the possibility of pheochromocytoma, the pink color of the fingers and the suggested hypersensitivity to mercury directed attention toward the diagnosis of acrodynia (Swift-Feer's disease, pink disease, dermatopolyneuritis). This is the more

* Rhodan in American nomenclature is rhodanate-thiocyanate. It is used in Europe for hypertension. (See Goódman, L.S. and Gilman, A.: *The Pharmacological Basis of Therapeutics*, ed. 2, Macmillan, 1955, p. 747.)

understandable as pheochromocytoma is uncommon in childhood. So far the number of confirmed cases in childhood amounts to about 26. The incidence of bilateral pheochromocytoma is much lower. In the case we have observed, surgery was out of the question because of the presence of very severe vascular and renal lesions. It is hoped that in the future the differential diagnosis will be much easier if the catecholamine test is carried out more often.

The intravenous administration of sodium amytal and even more so that of chlorpromazine may prove to be useful in the differentiation of the attack caused by catecholamine from that due to diencephalic pathology. This was done in case 5. However, the clinical pattern of the attack in this case was different from that seen in cases of pheochromocytoma. In the latter condition the hypertension is associated with blanching whereas in the diencephalic attack hypertension and tachycardia are associated with the phenomena suggesting parasympathetic discharges, such as flush, profuse perspiration, salivation, lacrimation, gastrointestinal rumbling, and headache of the vascular distension type. Laboratory studies have confirmed the differentiation of the two types of attack. In cases 5, 6, and 7, the estimation of urinary catecholamine was useful in excluding the diagnosis of pheochromocytoma which has been confirmed also by the successful treatment.

Summary

Since pheochromocytoma produces hypertension often curable by surgery, and since it is known that the incidence of this tumor is higher than earlier believed, the importance of diagnosis has increased. The pharmacological diagnostic tests which have been useful in some cases, but unreliable in others, are not without hazards. For this reason we have tested every patient suspected of having pheochromocytoma during the past few years for urinary output of catecholamine.

In the seven cases of hypertension exhibiting colorful clinical patterns and described in this paper, the diagnosis could be established on the basis of a careful analysis of the clinical picture, painstaking observation of the patient and evidence obtained from pharmacologic tests. Most important, the diagnosis could be established on the basis of the estimation of catecholamines in the urine.

It would appear worthwhile to make further trials with Hydergine which can be administered evidently with safety to combat temporarily spontaneous paroxysmal attacks or an attack produced by pharmacological diagnostic agents or provoked by the manipulation of the tumor during the course of surgical intervention.

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The Pure Form of Thyrotoxic Heart Disease

A Clinical and Pathological Study

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THE CIRCULATORY changes in patients with hyperthyroidism are well known since the classic description by Parry in 1786. Important contributions on this subject by Graves and Basedow in 1830, Stokes in 1854, Potain in 1863 and others are reviewed in an excellent paper by Ginsburg.[1] Following the demonstration that certain cases of heart failure could be controlled by thyroidectomy,[2] a number of publications concerning thyrotoxic heart disease have appeared. However, this is still a controversial subject in view of the conflicting opinions regarding the recognition of a specific type of heart disease which could be solely attributed to the effects of an overactive thyroid gland.

CARDIAC CHANGES WITH THYROTOXICOSIS

Myocardial Changes: In 1921, two cases of thyrotoxicosis associated with heart failure were studied by Goodpasture.[3] He emphasized the pathologic findings of myocardial degeneration, infiltration, necrosis and fibrosis which were considered as specific effects of the thyroid hormone in the presence of a generalized infection. These changes were also obtained experimentally by the same author.[4] Goodall and Rogers[5] in 1927, and Lewis[6] in 1932, observed a similar type of myocardial lesion in fatal cases of hyperthyroidism and believed that it was due to the direct influence of the thyroid secretion on the heart muscle. Duchosal and Henny in 1941[7] reported the case of a thyrotoxic patient with angina pectoris who died suddenly following thyroidectomy. There was no coronary artery pathology at autopsy but the myocardium showed degeneration with areas of interstitial fibrosis. In 1948 Lemos Torres[8] described two patients who died from thyrotoxic crisis. Autopsy disclosed cardiac changes characterized by serous myocarditis with fibroblastic degeneration, resulting from the effects of hyperthyroidism on the heart muscle. Other investigators[26–28] attempted to confirm the thyrotoxic origin of the histopathologic myocardial changes found in patients with hyperthyroidism, usually described as degenerative and interstitial lesions alternating with localized areas of necrosis. Many authors[9–13,29,30] disagreed with this interpretation, since they were unable to confirm these pathologic findings; they do not therefore recognize a specific type of myocardial lesion exclusively due to the effects of hyperthyroidism.

Heart Failure and Auricular Fibrillation: From the clinical standpoint, a number of publications have appeared since the paper by Likoff and Levine[14] describing the occurrence of cardiac failure in thyrotoxic patients in the absence of any other possible cause of heart disease. In 1949 Griswold and Keating[15] selected 35 cases with auricular fibrillation from a total of 54 thyrotoxic patients in heart failure. Twelve of these had no other associated forms of heart disease. It is interesting to note the comparatively low incidence of auricular fibrillation (65 per cent) in this series of decompensated thyrotoxic heart disease, since some authors[16] have found this arrhythmia in 90 per cent of their cases. It is

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also unusual that a regular sinus rhythm was maintained throughout the entire clinical course of 19 patients, 10 of whom had no other obvious cause of heart disease. This is most unusual in heart failure due to thyrotoxicosis.[17] Finally, a pure form of thyrotoxic heart disease completely reversible by thyroidectomy has been recognized by Gold.[18]

The appearance of auricular fibrillation during thyroid surgery in patients who had never previously presented this type of arrhythmia, and its occurrence in normal individuals following an overdose of thyroid hormone[19] are presented as positive evidence by those who accept the unequivocal cardiac effects of thyrotoxicosis. On the other hand, the reversion to a regular sinus rhythm is usually obtained by specific treatment of the endocrine dysfunction, although in a minority of cases it may be necessary to add quinidine in the immediate postoperative period.[16,20,21]

Angina Pectoris: An interesting aspect of this problem is the observation of cases of angina pectoris associated with thyrotoxicosis, in which the precordial pain, unresponsive to rest and to vasodilator drugs, responds to thiouracil. There is no correlation in such instances with the basal metabolic rates. Although the mechanism of action of the thyroid hormone is uncertain, the anginal syndrome probably results from myocardial anoxia due to the direct effects of thyroxin on the heart muscle. Thus, cardiac symptoms may appear in thyrotoxicosis in the absence of the typical hemodynamic changes of this condition.

ASSOCIATED ORGANIC HEART DISEASE

The majority of thyrotoxic patients in heart failure have demonstrable organic heart disease of other etiologies such as arteriosclerosis, hypertension, rheumatic fever or syphilis. Therefore, the above observations based exclusively on clinical data have been criticized since they lack adequate pathologic proof to exclude the possibility of coexistent organic heart disease. The inconsistent findings have led to a general skepticism regarding the structural cardiac changes attributed to hyperthyroidism. As a result, most authors have been inclined to doubt the existence of a pure form of thyrotoxic heart disease. However, as previously mentioned, a number of publications[3,5,7,8,14,15,18,22,23,25] seem to confirm the idea that hyperthyroidism *per se* may cause heart disease in the absence of any other etiologic factors.

Cardiac failure in hyperthyroidism results generally from the hemodynamic changes, although the normal heart usually adjusts exceptionally well to the circulatory strain which occurs under these circumstances. The fact that heart failure occurs as a rule in the older age groups may be considered as indirect evidence of coronary sclerosis, suggesting that hyperthyroidism acts merely as a precipitating factor of cardiac decompensation. Notwithstanding the controversial opinions as to the direct effects of the thyroid hormone on the heart muscle, the experimental studies[4,24] and the pathologic data in human cases[3,5,6,7,22,23] seem to confirm these effects which may cause myocardial necrosis and fibrosis, in addition to the so-called serous myocarditis.[8] It is our impression that the pure form of thyrotoxic heart disease is predominantly caused by direct myocardial damage which may be completely reversible spontaneously or following appropriate medication. Such cases can be identified not only by their clinical signs, but also by the favorable course in some instances, since a complete cure is to be expected by early adequate medication provided certain complications do not supervene. This type of thyrotoxic heart disease differs in many respects from the classical form of this condition, the latter being usually more resistant to therapy.

Because of the conflicting opinions regarding the existence of a pure form of thyrotoxic heart disease, we are presenting our personal observations in four cases and will discuss their unusual aspects from the clinical and pathologic standpoints. Despite the small number of cases in our series, we believe that they are sufficiently demonstrative, particularly in view of the pathologic data obtained in two of them.

Case Histories

Case 1. M. R. T., a 36-year-old Negro woman, was admitted to the Hospital dos Servidores do Estado on February 13, 1951 with a history of nocturnal cough

and chest discomfort since January 1949. She complained of intolerance to heat, palpitations and occasional bouts of dyspnea. In spite of these symptoms she was able to perform her usual household activities for five months, after which she was incapacitated by fatigue and palpitations appearing on exertion. Shortly thereafter she became pregnant. On the eighth month she had delivered a child which had not survived. This occurred approximately one year prior to her initial consultation. Following delivery she sustained profuse uterine hemorrhages which lasted five weeks. She complained of headaches and fever which occasionally reached 40°C. In February 1951 she became markedly dyspneic, edematous and required hospitalization.

Physical examination revealed a poorly nourished patient weighing 35 kg, with a slight exophthalmus and a visible nodular goiter (Fig. 1). The cardiac rhythm

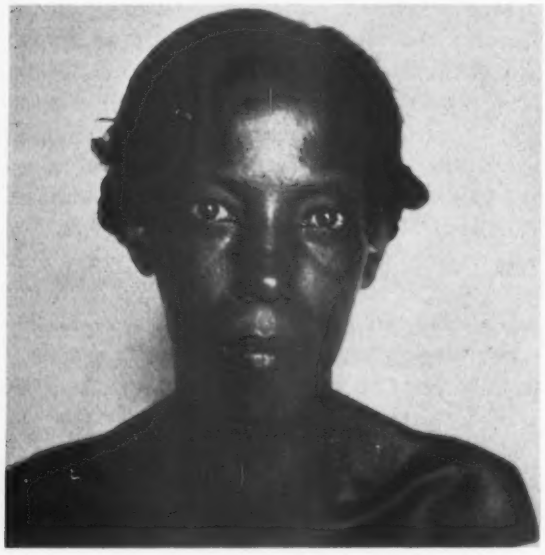

Fig. 1. Case 1. A 36-year-old patient with a nodular goiter, moderate bilateral exophthalmus and thyrotoxic heart disease.

was regular with a rate of 132 beats per minute. Pulsus alternans, engorgement of the jugular veins, and a blood pressure of 150/100 were observed. A forceful impulse of the cardiac apex was felt in the 6th left intercostal space. Auscultation revealed a grade II apical systolic murmur with muffled heart sounds. The 2nd pulmonic sound was louder than the aortic second sound. Circulation time (Decholin) was 8 seconds. The basal metabolic rate was +53 per cent. The liver extended three fingers' breadth below the right costal margin; there were signs of pleural effusion at the right lung base.

After three days of treatment with digitalis and mercurial diuretics she improved although the heart rate remained elevated for two weeks. On the 15th day of hospitalization all treatment was discontinued, notwithstanding which she became asymptomatic from the cardiovascular standpoint. After two months she left the hospital in excellent condition on antithyroid medication which was continued for 18 months. The patient finally agreed to submit to a subtotal thyroidectomy which was performed successfully on February 25, 1953. She was examined on January 8, 1954. She had no complaints, a regular heart rate of 84 beats per minute and a blood pressure of 120/80.

Roentgenologic examination (Fig. 2) initially revealed a marked increase in heart size with a slightly prominent left middle arch, an elevated left main bronchus observed in the left anterior oblique position, and esophageal displacement due to an enlarged left auricle in the right anterior oblique position. There were signs of pulmonary vascular engorgement. On the third day of hospitalization (February 16, 1951) there was a marked decrease in heart size and clear lung fields. After two weeks of treatment (February 28, 1951) the heart size became practically normal, and remained so in a number of subsequent examinations.

Electrocardiographic studies initially revealed signs of left ventricular enlargement with S-T segment and T wave changes partly due to digitalis. After digitalis had been discontinued for 40 days, the tracing showed evidence of left ventricular enlargement with flattened T waves in lead I and tall peaked T waves in leads II and III and V_5, suggesting a diastolic overload of the left ventricle. Subsequent tracings did not reveal any other significant changes.

Comments: The occurrence of advanced congestive heart failure in a young adult patient with a nodular goiter and symptoms of hyperthyroidism of two years' duration seems to indicate a close correlation between the cardiovascular and the endocrine conditions. It is probable that cardiac failure supervened in the period of aggravation of the thyrotoxic state. There was a favorable response of heart failure to digitalis and mercurial diuretics, and a spontaneous improvement of the hyperthyroid condition. This resulted in the disappearance of all signs and symptoms of heart failure.

The febrile condition suggests the possibility of an acute myocarditis due to an intercurrent infection. However, it is to be noted that heart failure was already under control when the fever was first noticed. On the other hand, the occurrence of a number of previous febrile episodes suggests that they may have represented thyrotoxic hyperthermia rather than recurrent infections. The absence of leukocytosis in repeated blood counts seems to confirm this viewpoint. The prompt and favorable response of heart failure to the usual therapeutic

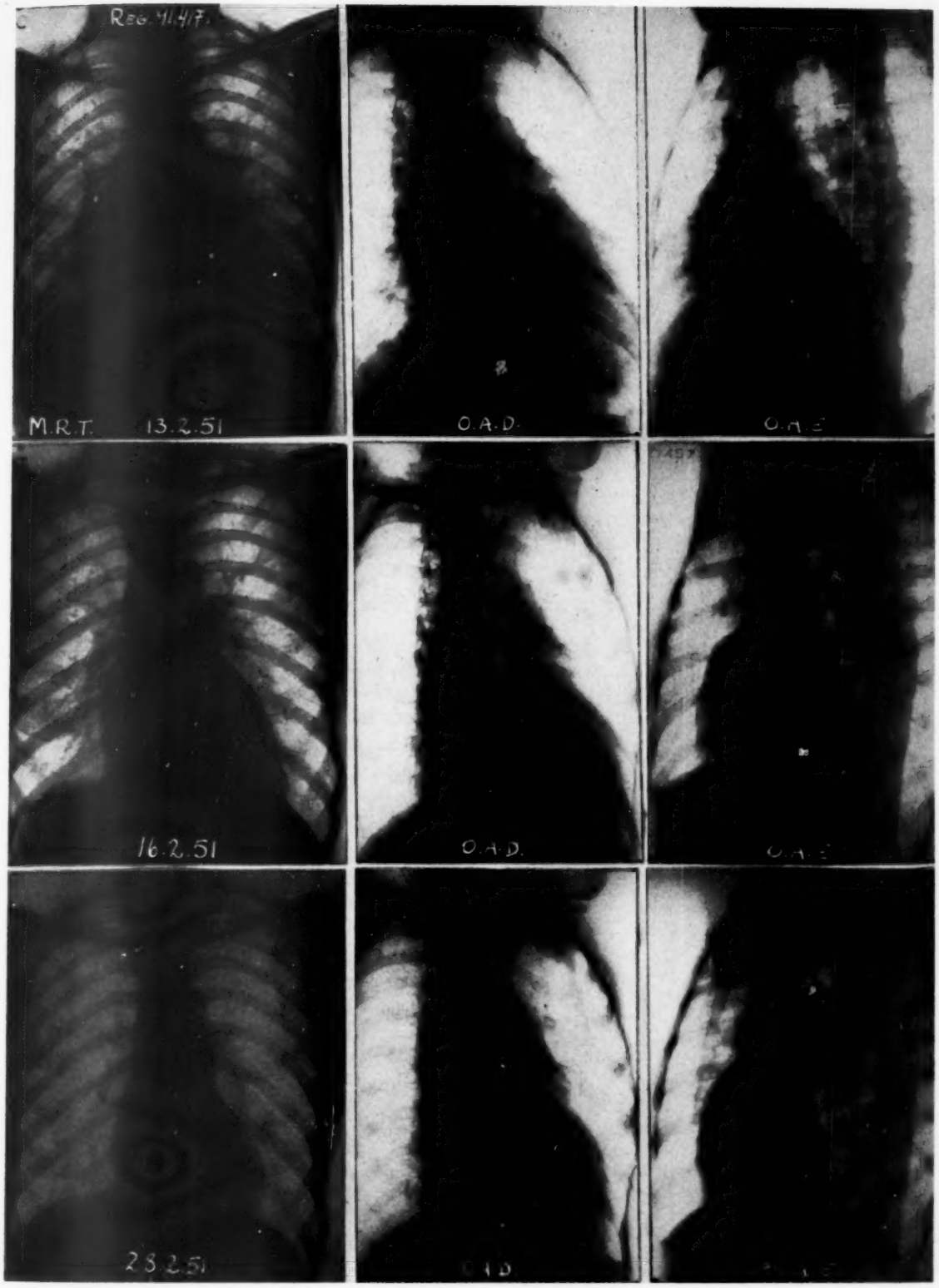

Fig. 2. Case 1. Serial teleroentgenograms of the heart. On Feb. 13, 1951 there is marked cardiac enlargement with definite dilatation of the left auricle as seen in the right anterior oblique view, in addition to signs of pulmonary congestion. On subsequent examinations there is a progressive decrease in heart size and clearing of the lung fields.

measures in this case also argues against the diagnosis of an infectious myocarditis which would be much more refractory to treatment and of more serious prognostic significance.

The electrocardiographic changes, although nonspecific, are extremely suggestive of hyperthyroidism, in view of the signs of a diastolic strain of the left ventricle, which occurs so frequently in this condition. The absence of auricular fibrillation during the entire clinical course is not unusual, since 35 per cent of such cases develop heart failure in the presence of a regular sinus rhythm.[15]

CASE 2. A. F. S., a 44-year-old white female, after a rapid weight loss of 40 pounds in two weeks, partly due to a self-imposed diet, began to complain of dyspnea on effort and at rest, nocturnal cough, chest discomfort, palpitations, edema and marked intolerance to heat. A small nodular goiter was noticed by her family physician at that time (March 1953). In view of her progressive symptoms, she was admitted to the Hospital dos Servidores do Estado on October 20, 1953, with the diagnoses of heart failure and thyrotoxicosis.

On admission she was orthopneic, had marked edema of the lower limbs, a rapid regular pulse of 116 beats per minute, a blood pressure of 120/50, engorged jugular veins, a gallop rhythm, a grade II systolic apical murmur and a grade I systolic murmur at the pulmonary area. The 2nd pulmonic sound was accentuated and a faint diastolic murmur was heard at the left sternal border. The liver was enlarged and slightly painful on palpitation. Moist rales were heard at both lung bases. The venous pressure was 21 cm of water. Circulation time (Decholin) was 8 sec. The basal metabolic rate was +62 per cent.

During the first week of hospitalization she remained at bed rest on a salt-free diet and mild sedation. At that time she had two attacks of auricular fibrillation, one of which required quinidine; however, a marked improvement was observed, particularly regarding dyspnea, tachycardia and edema of the lower limbs. Following these initial therapeutic measures she was given iodine solution and one week later, propylthiouracil. This combined therapy was continued for three weeks without further improvement in heart failure until digitalis and mercurial diuretics were administered shortly thereafter. On December 30, 1953, ten weeks after admission, she had a subtotal thyroidectomy. At that time her blood pressure was 130/70, heart rate 72 beats per min, venous pressure 14 cm of water and circulation time (Decholin) 12 sec. There were no further complications and the patient was discharged on the fifth postoperative day. She was seen three months later, and was asymptomatic, although all medication had been discontinued since her hospital discharge. In a second consultation one month later, she complained of a rapid gain in weight of 20 lb in three weeks. Postoperative hypothyroidism was suspected and she was given small doses of thyroid extract.

The first x-ray (Fig. 3) taken routinely several months before her present illness showed slight enlargement of the left ventricle. Two days after admission (October 22, 1953), there was a definite increase in heart size, a prominent pulmonary conus in the right anterior oblique position, and signs of hilar and peripheral pulmonary congestion. On November 11, 1953, after effective antithyroid and cardiotonic therapy, the heart size became normal with disappearance of all signs of pulmonary congestion. Subsequent roentgenograms after thyroidectomy revealed no significant changes.

A number of electrocardiograms were recorded. The initial tracing showed a sinus tachycardia of 115/min, and evidence of left ventricular enlargement. On October 27 a paroxysm of auricular fibrillation was recorded, and on November 11, normal sinus rhythm was restored at a rate of 78/min, with T wave changes attributed to digitalis. The first postoperative electrocardiogram on January 14, 1954, taken after digitalis had been omitted for 15 days, was practically normal. The tracing taken four months later showed a decrease in amplitude of the T waves, possibly due to a slight degree of postoperative hypothyroidism.

Comments: The interesting features of this case were the appearance of congestive heart failure and paroxysmal auricular fibrillation in a young adult patient with a nodular toxic goiter, in whom it was necessary to combine digitalis and antithyroid therapy to obtain complete cardiac compensation without further medication. After thyroidectomy she remained asymptomatic from the cardiovascular standpoint with complete normalization of the electrocardiogram and a normal heart on roentgen examination.

Cases of this type are often described as having latent coronary sclerosis, with hyperthyroidism acting as a precipitating factor of heart failure. However, we feel that arteriosclerotic heart disease can be ruled out in this normotensive female patient whose signs and symptoms of heart disease were completely controlled following subtotal thyroidectomy.

CASE 3. A. C. C., a 39-year-old Negro female with signs and symptoms of hyperthyroidism of 18 months' duration, entered the hospital with generalized edema which first appeared one year after her initial complaints. Three weeks prior to admission she became jaundiced and markedly dyspneic. On physical examination the patient was orthopneic and appeared severely ill with anasarca. The thyroid gland was diffusely enlarged with a predominance of the right lobe. The jugular veins were engorged and the carotid

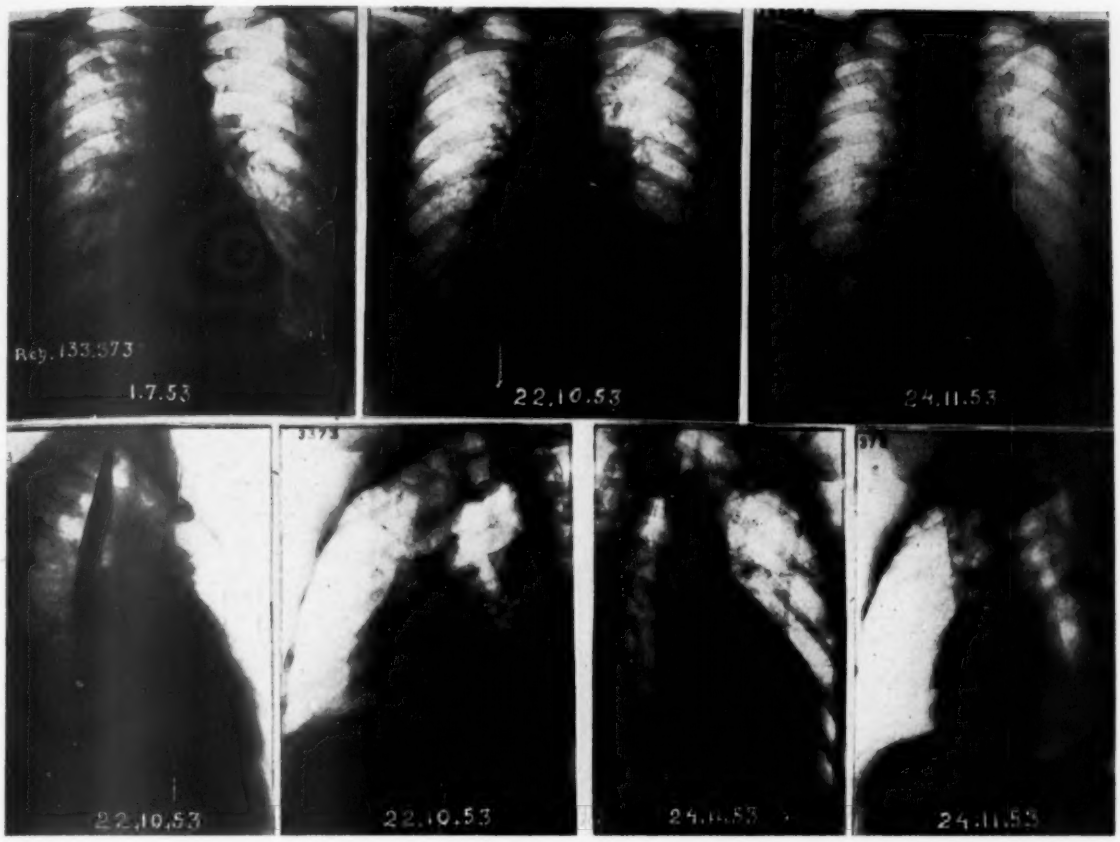

Fig. 3. Case 2. The first x-ray taken routinely before the occurrence of cardiac decomposition shows slight enlargement of the left ventricle and a prominent aortic knob. On October 22, 1953 there is a definite increase in heart size and signs of pulmonary congestion. One month later the patient was completely asymptomatic with a marked reduction in heart size and no evidence of pulmonary vascular engorgement, as observed roentgenologically.

arteries pulsated vigorously. The radial pulse was weak and irregular with a rate of 120 per minute. The blood pressure was 115/75. The cardiac impulse was felt in the seventh intercostal space at the left mid-axillary line. There were no murmurs and the heart rhythm was totally irregular. At the right lung base there were physical signs of pleural effusion although no rales were heard on either side. The liver was not palpable due to ascites.

The patient was digitalized orally with 12 cat units of digitalis leaf in 24 hours and was given mercurial diuretics, barbiturates and a salt-free diet. She was subsequently maintained on two units of digitalis daily. Notwithstanding some initial improvement with a considerable degree of dyspnea, she still complained of fatigue and anorexia. The cardiac arrhythmia persisted at a ventricular rate of 150 beats per min. On the third day of hospitalization, it was decided to administer digitalis by the intravenous route. In view of the slight degree of improvement she was given 30 drops of Lugol's solution daily in addition to digitalis. Following this treatment schedule, the heart rate decreased to 86. On the seventh hospital day she began to present signs of phlebothrombosis in both legs in addition to thrombophlebitis of the right arm, the latter as a result of an intravenous injection. On the following day she expired suddenly as a result of probable pulmonary embolism.

A number of laboratory tests were performed. Several urinalyses revealed the presence of bile pigments. Liver function tests were all abnormal and the serum cholesterol level was 80 mg %. In view of the marked degree of dyspnea, the basal metabolic rate was not determined. Roentgenologic examination (Fig. 4) showed cardiac enlargement with a predominance of the left ventricle and a prominent pulmonary conus. There was an obliteration of the left costophrenic angle. The electrocardiogram (Fig. 5) revealed auricular fibrillation with a ventricular rate of 200. The inverted T waves in lead I and over the left precordium were indicative of myocardial damage.

The main findings at autopsy consisted of an enlarged heart weighing 350 g with a dilated left ventricle, the free wall of which was thickened and measured 13

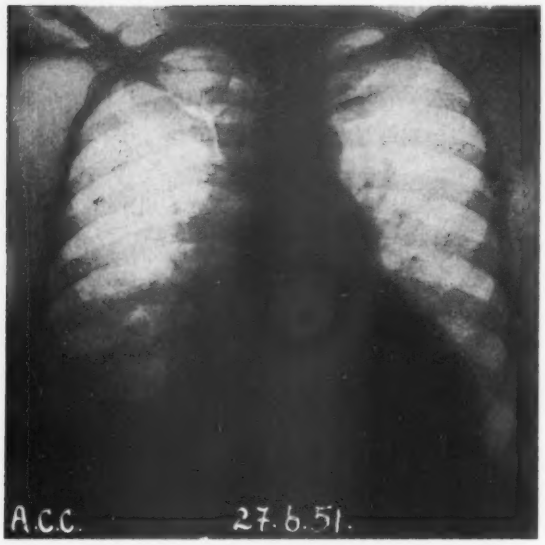

Fig. 4. Case 3. Cardiac enlargement with predominance of the left ventricle and a prominent pulmonary conus. There is a right pleural effusion.

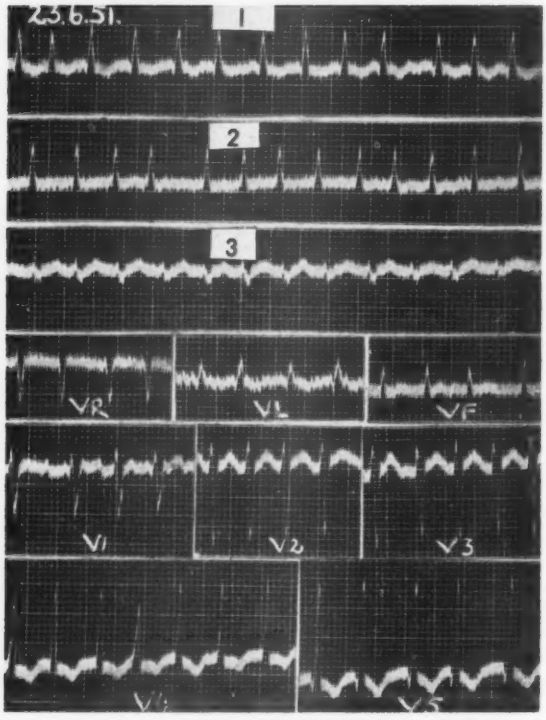

Fig. 5. Case 3. Electrocardiogram showing auricular fibrillation with a rapid ventricular rate of 200. Signs of left ventricular enlargement and myocardial damage.

mm. The coronary arteries were normal and patent throughout. Histological examination (Fig. 6) revealed dissociation of the myocardial fibers with irregular contour and diameter and areas of infiltration and interstitial fibrosis. The thyroid gland was enlarged and contained an adenomatous nodule. The vesicles were of various dimensions and were filled with a pink-stained colloid substance. There was a proliferation of the epithelial lining consisting of cylindrical and cubic cells. In conclusion, autopsy showed a serous myocarditis with incipient interstitial fibrosis, a diffuse hyperplastic goiter, serous hepatitis, acute cholecystitis and pyelonephritis.

Comments: This is certainly the most demonstrative case of all the cases. It exemplifies the pure form of thyrotoxic heart disease with advanced congestive failure and auricular fibrillation associated with a nodular toxic goiter. This patient showed a slight improvement only after combined digitalis and antithyroid medication. Death was presumably due to a massive pulmonary embolus most probably preceded by several minor episodes of a similar nature. Autopsy examination showed signs of serous myocarditis with incipient interstitial fibrosis and no evidence of any other type of associated heart disease. Although these myocardial changes are not considered pathognomonic, they have been previously reported in cases of severe hyperthyroidism.[8] According to Fahr,[31] the so-called "serous inflammation" in Basedow's disease affects the cardiac tissue more often than that of any other organ. These changes are only reversible in the initial stages since the more chronic cases develop interstitial fibrosis of the type designated by Rössle[32] as fibroblastic myocarditis which was already evident in our patient.

Case 4. L. M. S., a 40-year-old white housewife, was told in 1945 during a routine medical examination that she had a small goiter. Three years later she developed the first signs of hyperthyroidism, complaining of nervousness, palpitations and rapid weight loss. She denied having had shortness of breath or chest pain. Past history was non-contributory.

Physical examination revealed an extremely nervous, poorly nourished patient with marked pallor and a moist skin. A nodular goiter was distinctly visible protruding over the suprasternal notch. There was a slight degree of jaundice and marked bilateral exophthalmus. Axillary temperature was 37.4° C. The pulse was regular with a rate of 110 and the blood pressure was 170/80. There was a grade II systolic apical murmur and a grade I systolic murmur at the pulmonary area. In addition there was a faint diastolic murmur and accentuated 2nd heart sound at the pulmonary area. Vigorous arterial pulsations were noted in the neck. No rales were heard and the liver

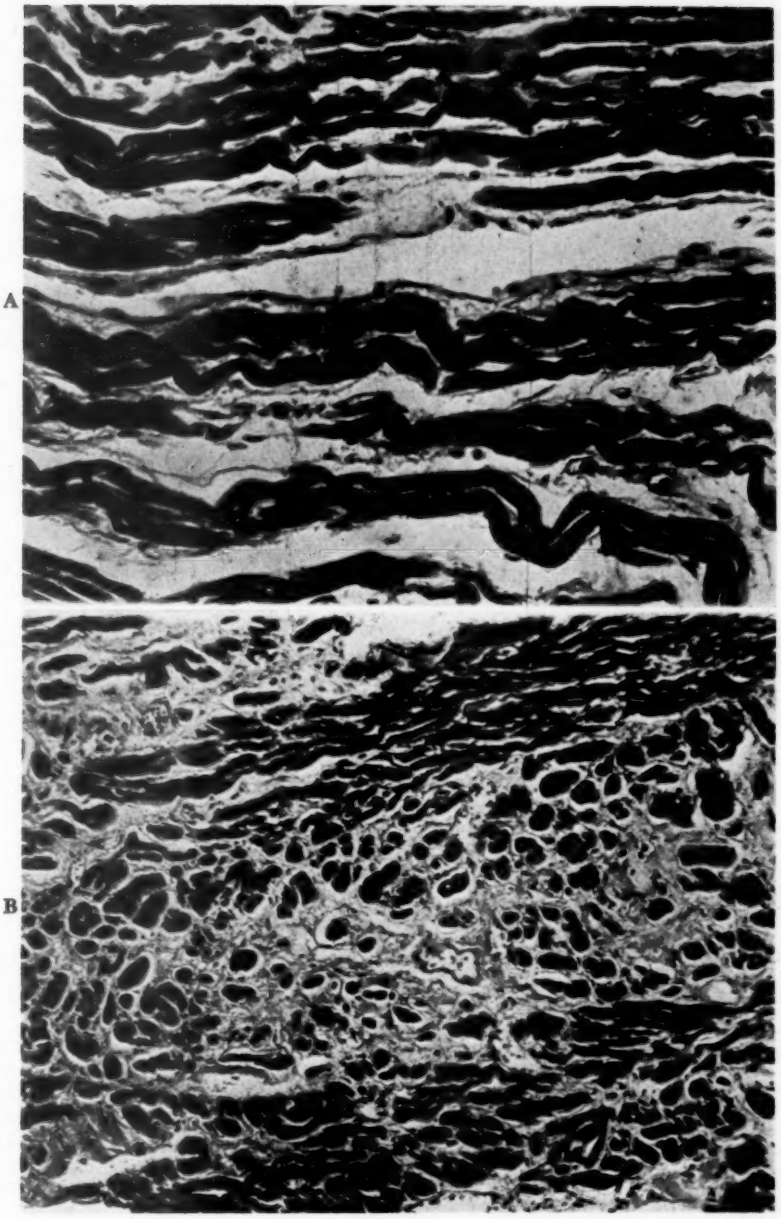

Fig. 6. Case 3. Microscopic section of the myocardium. (A) Dissociation of the cardiac fibers which are markedly irregular in shape and diameter with small areas of localized infiltration. (B) Interstitial fibrosis.

was not palpable. The BMR was markedly elevated and increased from +99 per cent to +123 per cent during a two-month period which preceded admission. There was a slight hypochromic anemia and the serum cholesterol was 162 mg %.

The patient was given 300 mg of propylthiouracil daily, in addition to vitamins and sedatives. One month later, iodine therapy was added in the form of 20 drops of Lugol's solution daily. This combination was continued for two weeks after which it was decided to interrupt the thiouracil. The patient markedly improved subjectively and objectively with weight gain and a reduction of heart rate to 80. The BMR decreased to +47 per cent. After two weeks of hospitalization she had a subtotal thyroidectomy. Her condition seemed to be quite satisfactory immediately after the operation, but she expired on that same day after a sudden episode of shock, despite all the thera-

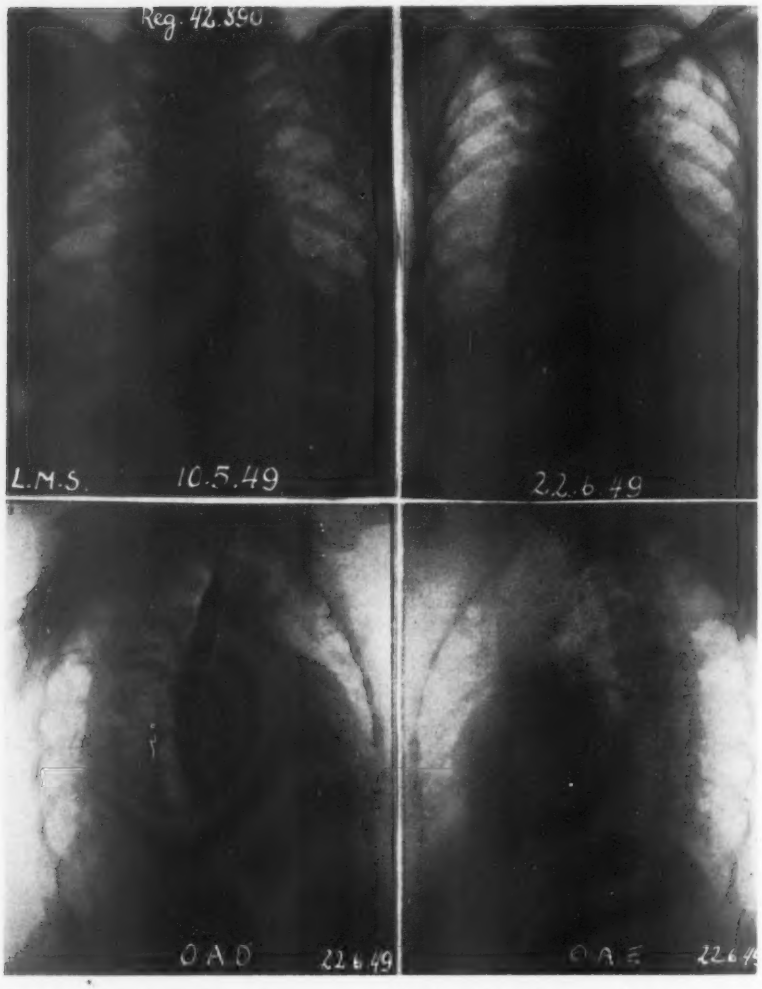

Fig. 7. Case 4. Teleroentgenogram of the heart showing a moderate increase in the cardiac area, with a prominent left middle arch and aortic dilatation. On June 22, 1949 there are signs of left auricular enlargement and a prominent pulmonary conus in the right anterior oblique view. The left ventricle is enlarged as seen in the left anterior oblique view.

peutic measures which were carried out immediately.

Among the pertinent laboratory data, a chest x-ray (Fig. 7) revealed a moderate increase in heart size, a prominent aortic arch and a slightly prominent left middle arch. A second roentgenogram six weeks later showed signs of left ventricular and left auricular enlargement. The electrocardiograms (Fig. 8) showed incomplete right bundle-branch block, P wave changes suggestive of left auricular enlargement, and tall R waves with positive T waves over the left precordium. These changes were interpreted as indicating a diastolic strain of both ventricles. At autopsy the heart was enlarged, weighing 395 g, with no abnormalities involving the pericardium, the endocardium or the heart valves. The coronary arteries were entirely normal. There was no evidence of myocardial fibrosis. The free wall of the left ventricle measured 14 mm. In addition, there were bilateral pleural fibrosis, pulmonary emphysema, splenomegaly, and a colloid goiter with parenchymatous hyperplasia as shown by the histologic examination performed after thyroidectomy.

Comments: This case was included as an example of isolated left ventricular hypertrophy occurring in a hyperthyroid patient without evidence of heart failure or auricular fibrillation. With all other etiologic factors of heart disease ruled out by autopsy, the cardiac hypertrophy was attributed to hyperthyroidism. There are a number of reports[11,26,33,34] concerning the frequent occurrence of cardiac hypertrophy in patients with thyrotoxicosis. Some authors

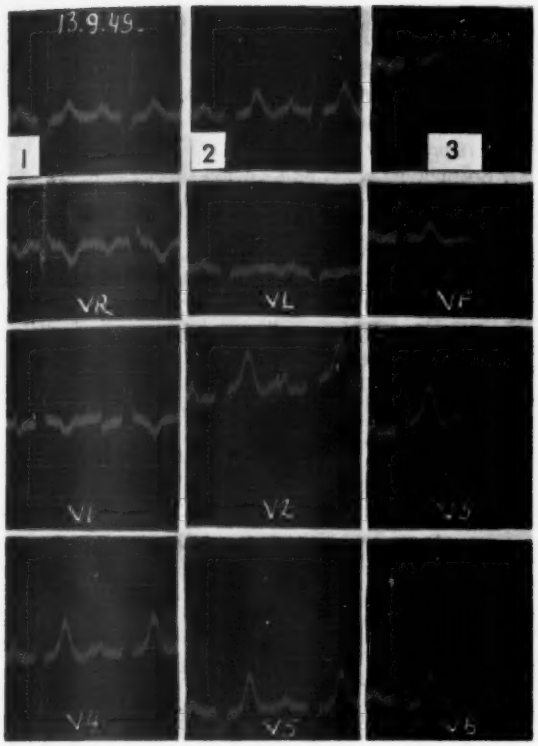

Fig. 8. Case 4. The electrocardiogram shows P wave changes indicating left auricular enlargement, in addition to incomplete right bundle branch block. The R waves are increased in amplitude in V_5 and V_6 with tall peaked T waves. These changes suggest a diastolic strain of both ventricles.

believe it is due to an associated type of heart disease such as arteriosclerosis or hypertension. According to others, cardiac hypertrophy may result from hyperthyroidism *per se*, either as a result of the hemodynamic changes or as an effect of the thyroid hormone which, according to Raab,[25] sensitizes the heart to the adrenosympathogenic catecholamines.

Discussion

On the basis of our experience with these four cases we believe that there is such an entity as pure thyrotoxic heart disease, although it is a relatively uncommon condition. In contrast to the number of cases of severe hyperthyroidism without cardiac involvement and the frequent occurrence of associated types of heart disease in patients with thyrotoxicosis in heart failure, there are comparatively few proven instances of so-called isolated thyrotoxic heart disease. This condition may appear either as a simple cardiac hypertrophy or progress to the more advanced picture of heart failure. The latter may be completely reversible if appropriate therapy is given in the early stages of the disease. It is our impression that heart failure due solely to thyrotoxicosis results mainly from the effects of the thyroid hormone on the heart muscle. The clinical picture differs somewhat from the usual form of thyroid heart disease in which the hemodynamic changes affect a previously damaged heart. This is a more chronic condition which does not respond completely to therapy in view of the underlying organic changes which are already present. On the other hand, the pure form of thyrotoxic heart disease may be completely reversible, since the initial changes due to serous myocarditis often respond to appropriate medication, provided fibroblastic changes have not yet occurred.

It is well to recall that this condition is similar to cardiac beriberi[35] which, in its advanced stages, may equally lead to myocardial fibrosis and simulate other types of degenerative heart disease.[36] Finally, it should be emphasized that the two forms of thyrotoxic heart disease which we have just described are not always sharply differentiated clinically, since a number of intermediate types are apt to occur.

Summary

Four cases of thyrotoxic heart disease are presented in which cardiac involvement was attributed solely to hyperthyroidism in the absence of any other etiologic factor. Heart failure occurred in three instances while the fourth patient remained compensated throughout the entire clinical course and showed left ventricular hypertrophy at autopsy. In addition to this case, necropsy examination was done in one of the patients with heart failure and revealed dissociation of the myocardial fibers and interstitial edema.

The two remaining cases survived following treatment with digitalis, antithyroid drugs and finally subtotal thyroidectomy with subsequent normalization of the entire clinical picture, including the electrocardiographic and roentgenologic abnormalities.

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A Clinico-Pathologic Study of Cor Pulmonale with Heart Failure*

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THE "mystery of cor pulmonale," as expressed by Cournand,[11] still awaits solution. Although a great deal of meritorious research work has been achieved during the last years, the pathogenesis of this condition is not yet fully understood, the criteria for early diagnosis are still inadequate, and the results of therapy are far from satisfactory. One of the multiple factors for this state of affairs is the close interdependence of respiratory and circulatory disturbances.

There is also a deplorable lack of agreement on terminology. Whereas to most authors cor pulmonale means nothing more than right ventricular hypertrophy consequent to chronic bronchopulmonary disease, others include the notion of right heart failure in this term, although it would be more appropriate to apply the expression "cor pulmonale decompensatum" or "cor pulmonale with heart failure" to this latter condition. This disagreement on diagnostic criteria and terminology has led to further confusion since the data on this subject in the literature have been mostly derived from clinical material lacking homogeneity and adequate nosologic classification.

Although morbid anatomy may solve these problems, this field of research has been sadly neglected during the last decade, while functional pathology has come into its own. To this branch of science we owe much remarkable information on the various aspects of cor pulmonale. There are only a few studies based on necropsy material.[9,25,30,36,48] The Italian authors[9,36] have been exclusively concerned with cases of tuberculous origin; the paper by Wells[49] deals with cor pulmonale as a consequence of pneumoconiosis; the extensive material of McKeown[30] and of Könn[25] has been worked up only from the anatomic angle; Walzer and Frost's publication[48] includes only a little material without sufficient clinical detail. We hope, therefore, to fill a real gap by discussing some questions of pathogenesis and symptomatology derived from the study of our material consisting of 67 cases verified at necropsy in the course of the last four years.

The anatomic diagnosis of cor pulmonale with heart failure has been based on (a) the presence of isolated hypertrophy and dilation of the right ventricle; (b) absence of any cardiac alteration that may account for this hypertrophy; (c) presence of chronic bronchopulmonary disease; and (d) congestion of parenchymatous organs. The clinical diagnosis has been confirmed at necropsy in each case. This shows that the differentiation of cor pulmonale with heart failure from other forms of heart failure or from ventilatory insufficiency is well within our capabilities at least in this terminal stage, although the difficulties of early diagnosis have been rightly stressed.[10,26]

PATHOGENESIS

BRONCHOPULMONARY DISEASE

Table I indicates the types of bronchopulmonary disease present. Our findings fail to confirm the views of Bayliss[4] and Gram,[33] according to which emphysema accounts for the initial complaints in almost every case of nonvascular origin.[28,31] Idiopathic generalized em-

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TABLE I

Classification of Chronic Bronchopulmonary Disease in Patients with Cor Pulmonale and Right Heart Failure

Bronchopulmonary disease	Number of patients	Secondary emphysema	
		Present	Absent
Pulmonary tuberculosis	11	5	6
Thoracic deformities	14	13	1
Tubercular kyphoscoliosis	2	—	2
Pulmonary fibrosis	15	9	6
Idiopathic emphysema	21	—	—
Other morbid entities	4	3	1
Total	67	30	16

physema has been found in about 30 per cent of our cases, a similar incidence to that reported by Griggs *et al.*[20] Secondary emphysema consecutive to other morbid conditions, such as kyphoscoliosis, fibrosis, etc., or as compensation for loss of parenchyma, was present in an additional third of our cases. In 16 cases, 14 of which belonged to the group of tuberculous or nonspecific fibrosis, no trace of emphysema, generalized or focal, was found, whereas it was present in all but one of the cases of kyphoscoliosis. Evidence of pneumoconiosis has been found in four cases of the fibrosis group; recurrent pneumonitis was the most conspicuous feature in the history of the other cases. In the tuberculosis group, bilateral pleural concretion with generalized fibrosis could be demonstrated in nine cases, and mere fibrosis and active fibro-ulcerous process in one case.

These findings support the view of Blasi and Catena,[6] according to which pleuro-pulmonary adhesions play a dominant role in the development of cor pulmonale, owing to the limitation of lung expansion. However, caution is recommended in interpreting our findings, since active tuberculosis is infrequent in the necropsy material of general medical wards; recent haematogenic dissemination present in one of our cases has been considered only as an antemortem complication.

Chronic bronchitis could be demonstrated in all the cases of emphysema and in the majority of the cases belonging to the fibrosis group. The question, which of the two processes—bronchitis or emphysema—should be regarded as primary, is beyond the scope of this paper; the classification of Table I has been used for the sake of expediency.

Bronchiectasia has been found in 14 patients (eight cases of fibrosis, three of emphysema, two of kyphoscoliosis, and one of tuberculosis). Contrary to Samuelsson,[39] Orie *et al.*[34,35] Turiaf *et al.*[46] we do not believe that cor pulmonale with failure is a common consequence of bronchial asthma. Schubert and Fischer[42] have recorded three such cases, associated with severe emphysema confirmed at necropsy, during an observation period of 30 years. In this period there were registered 13 deaths in status asthmaticus, a fairly rare outcome of bronchial asthma. We agree with Hajós[21] that cor pulmonale is the consequence of the complicating chest disease rather than of the asthma. The characteristic anatomic picture[17,27] was not found in any of our cases. Neither did we have any case of primary vascular cor pulmonale with fatal outcome under our care during these four years. The increasing number of publications relative to this subject is more proportional to its interest than to its incidence.

OTHER CARDIOVASCULAR DISEASES

Other cardiovascular disturbances may also play some part in the development of cor pulmonale with heart failure. Coronary arteriosclerosis was present in 25 cases, hypertension and aortic valve disease without noteworthy hypertrophy or dilation of the left ventricle in 10, syphilitic aortitis in 3. The incidence of associated heart disease was not comparable in the different groups. It was present in nine of 15 cases of pulmonary fibrosis, absent in the majority of the kyphoscoliosis group (7 out of 12 cases) and of the tuberculosis group (8 out of 13 cases).

Nonpulmonary heart disease, the frequency of which has been justly emphasized by White[50] and others, is not without interest from the viewpoint of pathogenesis. It might give the clue to the intricate question: why does right heart failure occur only in some of the cases with severe chronic pulmonary disease? No close correlation can be demonstrated between the grades of ventilatory and circulatory damage.[3]

TABLE II
Age of Cor Pulmonale Patients at Death

Age group	Emphysema	Pulmonary fibrosis	Tuberculosis	Chest deformities	Other	Total
–40	—	—	1	—	—	1
41–50	—	1	—	—	—	1
51–60	5	6	3	5	1	20
61–70	7	4	5	5	1	22
71 80	8	3	2	6	1	20
81–	1	1	—	—	1	3

Patients incapacitated by severe dyspnea rarely develop heart failure.[14] Perhaps, when faced with a case of long-standing chest disease we might be able to forecast the likelihood of heart failure from the extent of pre-existing myocardial damage.[7,8,22] Anatomic evidence bears out the role of this mechanism in 50 per cent of our cases, while extracardiac factors, such as disturbances of cerebral metabolism,[13] vascular compression in consequence of increased intrathoracic pressure,[23,38] and other still less clear mechanisms may account for the rest.

OTHER PREDISPOSING CAUSES

Age: Cardiac failure generally follows long-standing pulmonary disease. Signs and symptoms of ventilatory insufficiency were present for over three years in 60 per cent, and for over one year in 80 per cent of our material. This is reflected in the age distribution: with only two exceptions the age at death was equally divided among the sixth to eighth decades (Table II). The average age in the emphysema group was higher than that of the rest, the number of cases in the age group over 70 being almost twice as high as the other types of chest diseases. Remarkable is the great number of kyphoscoliotic patients in the highest age groups as compared with the earlier series of Chapman *et al.* who found a life expectancy of only 30 years. The existence of new therapeutic tools especially for the control of bronchopulmonary infection may be a clue to the changed character and prognosis of this disease (Gray[19]).

Sex: The 3:1 sex distribution of our cases (50 males, 17 females) confirms earlier published data. Seventy-six per cent of the men dying with cor pulmonale with heart failure as compared to 56 per cent of our general medical ward patients were industrial workers, evidence supporting the opinion of Delius[13] on the role played by physical work in the development of cor pulmonale.

Tobacco: Another pathogenetic factor widely discussed these last years is smoking. The importance of cigarettes in the etiology of chronic bronchopulmonary disease was stressed by several authors.[1,29,37] We have reliable data of the maximum daily cigarette consumption of 61 patients in our series (Table III). Forty per

TABLE III
Maximum Cigarette Consumption in Cases of Cor Pulmonale with Failure

Number of cigarettes per day	Emphysema		Fibrosis		Other broncho-pulmonary disease		Total	
	Male	Female	Male	Female	Male	Female	Male	Female
0	5	4	2	1	3	7	10	12
1–10	3	—	4	—	5	1	12	1
11–25	2	—	4	1	7	1	13	2
25+	4	—	1	—	5	1	10	1

cent were nonsmokers; the great majority of our female patients belong in this category, but almost one-half of the male group also consisted of nonsmokers or light smokers, the latter never having consumed over 10 cigarettes daily. The proportion of heavy smokers was about 20 per cent among the emphysema as well as among the kyphoscoliosis and tuberculosis patients, although cigarettes did not play a leading part in the pathogenesis of the latter groups. Thus, we consider the role of smoking to be incidental in the development of cor pulmonale with heart failure.

Signs and Symptoms

Dyspnea: This was the chief complaint of most patients. It was completely absent in six; one patient suffered shortness of breath only on exertion; 60 patients had respiratory distress at complete bed rest. The change in character of the former exertional dyspnea to dyspnea at rest is the most important sign of the development of cardiac failure. Less frequently it may also arise in chronic bronchopulmonary disease or cor pulmonale without heart failure,[26] especially in the presence of ventilatory insufficiency following acute respiratory infection. Persistent dyspnea, however, although not pathognomonic, should direct our attention towards the diagnosis of cor pulmonale with failure. We cannot share the opinion of those authors[16,45] who seldom find noticeable shortness of breath in right heart failure of pulmonary origin. This is valid only for orthopnea on the absence and mechanism of which we commented in an earlier paper.[18] Respiratory distress is entirely absent in about 10 per cent of the cases, in consequence of the swiftly developing hypercapnic narcosis.

Edema: This was present in 32 cases. The diagnostic value of this sign is limited by its absence in half of our cases of cor pulmonale with failure and its high incidence in hypoproteinemia complicating chronic pulmonary disease without heart failure. This might be caused by systemic amyloidosis (three cases in our material) or hypoxemic liver damage.

Other Cardiac Symptoms: Other complaints, such as cough, lack of strength, etc. are those of the underlying pulmonary disease. Anginal precordial pain which has been considered an important sign of pulmonary hypertension,[3,47] was present in only six cases.

Cyanosis was absent in 15, edema in 18, enlargement of the liver in 26 and cardiomegaly in 8 cases; in none were all these four prominent symptoms of heart failure missing.

Disturbances of Cerebral Blood Supply and Metabolism: These disturbances are of primary importance in the pathophysiology of cor pulmonale with heart failure.[5] The pertinent clinical symptomatology does not receive its full attention in the literature. Disturbed sensorium, from stupor to deep coma, was present on admission in one-third of our group (23 cases) and developed during the latter course of hospital treatment in most other patients. Symptoms of cerebral damage, including neurologic disorders such as hemi- or tetraplegia, belong as closely to the clinical picture of cor pulmonale with heart failure as do those of congestive failure.

Laboratory Findings

No investigative procedure likely to overtax the circulation or requiring close cooperation of the patient will give reliable results in cases of cor pulmonale with severe heart failure. This was why we abstained from cardiac catheterization in this series, although it is of diagnostic aid in the initial stage of the disease. In some of our cases we even had to dispense with x-ray and electrocardiographic examinations, 8 patients having died on the day of admission and 13 in the course of the next two days. Dynamic tests of pulmonary function were either not performed or regarded as valueless in a great number of cases, since the patients were not in a physical or mental condition to cooperate.

Blood Pressure: Systemic arterial pressure was normal in the great majority of cases. Moderately elevated diastolic levels (not exceeding 110 mm Hg) were present in 11, higher levels in only one patient.

X-Ray Examination: Chest x-ray showed heart shadows of normal size in 7 patients, enlargement to the right in 28 and to the left in 19. Fluoroscopy in oblique views was infrequently performed because of the physical incapacitation of most patients. Thus we possess

incomplete data about the size of the individual cardiac chambers and great vessels. Enlargement to the left was caused by right ventricular dilation in every case amenable to detailed study.

Electrocardiogram: The electrocardiogram cannot yet yield evidence of heart failure, but only of ventricular strain. Even this was missed by previous workers[26,41] in one-third to one-half of their material. Its incidence is higher among patients with excessive pulmonary hypertension.[43] Thus the pattern of right ventricular strain is more frequently found in cor pulmonale with heart failure than in cor pulmonale without failure. Accordingly, in none of our patients with severe pulmonary heart disease was the electrocardiogram entirely normal. Auricular changes were very frequent; normal P waves were encountered in only 17 cases, nodal rhythm in 2, auricular fibrillation in 11, and tall, peaked P waves in the rest. Auricular fibrillation is considered as an unusual occurrence in cor pulmonale with heart failure, especially in uncomplicated cases.[45,48] The incidence of coronary arteriosclerosis is high, however, in conformity with the age distribution of the patients. It was present in 10 of our 11 fibrillating patients at necropsy. Other forms of arrhythmia were less frequently observed: ectopic beats, auricular and ventricular, were registered in several cases.

The common pattern of right ventricular hypertrophy in the standard leads was present in 23 or only one-third of cases. The electrocardiogram of five patients with coronary sclerosis showed a left ventricular strain pattern in the standard leads; no left-sided hypertrophy or dilation was found at necropsy. Low voltage, which in combination with P pulmonale is considered characteristic of cor pulmonale[26] was seen in only five cases.

In 31 cases we recorded the precordial leads V_1 through V_8. R waves in V_1 exceeding 5 mm, considered as a most important sign of right ventricular hypertrophy by Schaub *et al.*,[41] were found in only seven cases. The incidence of deep S waves (over 5 mm) in V_5 and shifting of the transitional zone to the left were higher (15 and 18 cases, respectively), thus yielding valuable proof of right ventricular hypertrophy.

Polycythemia: Other laboratory findings obtained in a considerable number of cases are summarized in Table IV. Polycythemia is

TABLE IV

Laboratory Data in Cases of Cor Pulmonale with Failure

Polycythemia	Present	11
	Absent	50
Venous pressure	Under 100 mm H_2O	4
	Over 100 mm H_2O	10
Vital capacity	1,000 ml	9
	1,000–1,500 ml	5
	1,500+ ml	2
Ether circulation time	Normal	5
	Prolonged	18
Lobeline circulation time	Normal	17
	Prolonged	7
Sputum culture	Nonpathogenic flora	8
	Pathogenic flora	8

considered by many authors to be characteristic of cor pulmonale with heart failure especially of its anoxemic form, since anoxemia has been supposed to play a significant role in the pathogenesis of polycythemia.[12] In contradistinction to this traditional view and in conformity with more recent data[15,34,35,44,51] polycythemia could be demonstrated in only one-sixth of our cases. It is not clear why polycythemia is absent in the majority of cases with cor pulmonale with heart failure in contrast to other hypoxic conditions. We may assume, however, that the number of erythrocytes is determined by the balance of the trend toward anemia due to chronic pulmonary infection and the opposite influence of hypoxemia.

Circulation Time: The literature contains divergent and partly contradictory statements on circulation times in this disease. Prolongation of the ether (arm-to-lung) time and normal arm-to-tongue time was described by Scharf,[40] while an enhanced difference between the two was reported by Zipp.[52] Normal values of both circulation times with high venous pressure were considered by others[24] to be characteristic for cor pulmonale with failure. Prolonged ether and normal lobeline times were present in the majority of our cases with numerous exceptions. Increased arm-to-lung time seemed to be the rule. However, normal values may be present

as a result of previous shortening of the circulation time consequent to chronic chest disease.

Venous Pressure: Venous pressure was elevated in over two-thirds of the cases studied. The diagnostic value of the test is limited by the high incidence of similar elevated figures in uncomplicated emphysema as well as of normal pressures in some cases of cor pulmonale with heart failure.[26,32]

Vital Capacity: Reliable and reproducible estimations of vital capacity could be carried out only in 16 cases. In five cases severe thoracic deformity, partly a consequence of extensive pulmonary resection, accounted for the extremely low values. In the rest, no other cause than superimposed right heart failure could be demonstrated.

Bacterial Cultures: Normal nonpathogenic microbial flora was present in the sputum of one-half of the cases investigated bacteriologically, and pathogenic micro-organisms in the other half. Bacteria resistant to the common antibiotics (proteus, pyocyaneus, candida albicans, etc.) prevailed among the latter. This evidence supports the opinion of numerous authors that acute pulmonary infection is the main factor in precipitating the development of heart failure. In view of the etiologic and symptomatic variability of cor pulmonale with heart failure, no exclusive significance should be attributed to this or any other factor.

Summary and Conclusions

(1) The pathogenesis and clinical picture of cor pulmonale with heart failure have been studied in 67 cases verified at necropsy.

(2) Idiopathic emphysema was present in only 30 per cent of the cases; lung fibrosis, pleuropulmonary tuberculosis and thoracic deformities were the causes in the rest. Secondary emphysema was found in the majority of the cases of thoracic deformity but was less common in the other entities.

(3) Pleuropulmonary adhesions appeared to play an important role in the development of cor pulmonale by limiting lung expansion.

(4) The incidence of associated cardiovascular disease of other causes, usually coronary sclerosis, was high. The resulting myocardial disease appeared to play an important role in the development of cor pulmonale in patients with chronic pulmonary or chest disease. This was supported by the observation that all our patients but two were over 50 years of age. Generally the emphysema patients were older than patients with other diseases.

(5) Industrial workers prevailed in our series. Smoking was not an important etiologic factor.

(6) Dyspnea at rest was the most frequent symptom. The progression of dyspnea on exertion to dyspnea at rest is the most important sign of the development of cardiac failure. Any one of the other signs of heart failure, such as cardiomegaly, cyanosis, liver enlargement and edema, may be absent in any single case, but in none of our patients were all of them absent.

(7) Disturbance in cerebral circulation and metabolism manifested by stupor progressive to coma developed in most of the patients. These manifestations have not received sufficient emphasis in the past.

(8) The electrocardiogram was abnormal in practically all cases. The most frequent findings were P pulmonale, right ventricular hypertrophy pattern, shift of the transitional zone to the left and deep S waves in the left-sided precordial leads. Auricular fibrillation, a common finding, was probably a manifestation of underlying coronary sclerosis.

(9) Polycythemia was absent in five-sixths of the cases despite the severe anoxemia. The cause for this is not clear but may reflect the tendency to anemia as a result of chronic pulmonary infection.

(10) A prolonged arm-to-lung (ether) circulation time with a normal lobeline time (arm-to-brain) was the general rule. The venous pressure was elevated in two-thirds of the cases.

(11) Pathogenic bacterial flora was cultured from the sputum in one-half the cases. This emphasizes that acute pulmonary infection is an important precipitating factor in patients with chronic pulmonary disease.

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Oral Nicotinic Acid for Hyperlipemia*

With Emphasis on Side Effects

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EXPERIMENTAL and clinical evidence indicates that an abnormal concentration of lipids in the blood bears a relationship to the development of atherosclerosis in some individuals. Consequently, various methods have been tried to lower the concentration of the different lipid fractions of the blood. Low fat diets, dessicated thyroid, vegetable sterols, estrogens, preparations of linoleic acid, etc., all have some lowering effect on the lipids. However, the results have been variable and limited, often with disagreeable side effects.

Altschul and associates[1] demonstrated that the serum cholesterol could be reduced in normal and hypercholesterolemic individuals after ingestion of 1 to 4 g of nicotinic acid. Later he also demonstrated[2] the prevention of atheroma formation in rabbits fed a cholesterol compound with nicotinic acid. Parsons and Flynn[3] gave 24 patients with hypercholesteremia 3 to 6 g of nicotinic acid daily with a 66.7 per cent average reduction in blood cholesterol. They also demonstrated that niacinamide was ineffective.

This investigation was instituted to confirm the results of Altschul and Parsons and Flynn and to expand upon the clinical experience of the use of the drug in such large doses. In addition our observations show that the side effects and complications are not quite as benign as the previous reports might lead one to believe.

METHODS AND MATERIAL

The study comprised 48 private patients with laboratory evidence of hypercholesterolemia. They were under constant observation by the authors for two months to eight years prior to the study. Their ages varied between 35 and 70 years. Seventeen were females and 31 males. Thirty-six had coronary disease, 14 hypertension, 7 diabetes, 17 xanthelasma, and 2 xanthomata. Most were on a low fat diet.

Nicotinic acid was administered as either 500 mg tablets or in a proprietary capsule containing 375 mg nicotinic acid, 50 mg ascorbic acid, 2.5 mg riboflavin, 5 mg thiamine mononitrate, 1 mg cobolamine concentrate, 0.5 mg pyridoxine HCl and 2.5 mg calcium pentothenate. The tablets or capsules were administered after meals in an attempt to slow absorption and decrease the side effects. The dosage was gradually built up to 3,000 mg per day if tolerated. The largest quantity given was 4,000 mg of nicotinic acid per day in contrast to the 6,000 mg given by Parsons *et al.*[4]

Lipid studies were done at monthly intervals. Cholesterol determinations were performed in all cases (method of Sperry[5]). The phospholipids (Youngsburg[6]), and the total lipids (Sperry[7]) were also followed in many. In addition, liver function tests were obtained in quite a few of the cases. The period of observation while on nicotinic acid ranged from one to ten months.

RESULTS

Side Effects (*Table I*): All cases demonstrated various degrees of flushing, mostly around the head and neck. In about one-third it was severe enough to cause withdrawal of the nico-

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TABLE I

Incidence of Side Effects in 48 Patients Treated with Large Doses of Nicotinic Acid

Side effects	Number of patients	%
Flushing	48	100
Severe enough to stop medication	16	32
Gastrointestinal distress	19	40
Pruritis	12	25
Unusual nervousness	6	12
Panic reactions	2	4
Dry mouth	2	4
Other		
(a) Diabetes worse	1	
(b) Body odor stronger	1	
(c) Hypothyroidism	1	

tinic acid. Many of the patients developed a tolerance to the flushing and in some it eventually disappeared completely. Missing a dose or two of the medication resulted in exaggeration or return of the flush, but this was usually temporary. Conjunctival injection was seen in some cases during the flush. In general, the intensity of the flush varied greatly from patient to patient but the hypolipemic results were in no way related to the degree of flushing.

Pruritis occurred in about 25 per cent of the patients. Gastrointestinal distress occurred in about 40 per cent of the patients. In two instances there was a reactivation of the symptoms of peptic ulceration. None of the patients had myocardial infarction but two developed congestive failure; this probably was coincidental. Ten per cent of the individuals complained of unusual nervousness and two developed panic reactions while on the nicotinic acid. Two patients had dry mouths and several thought they had dry skin. In one case, existing diabetes became worse and one individual noted

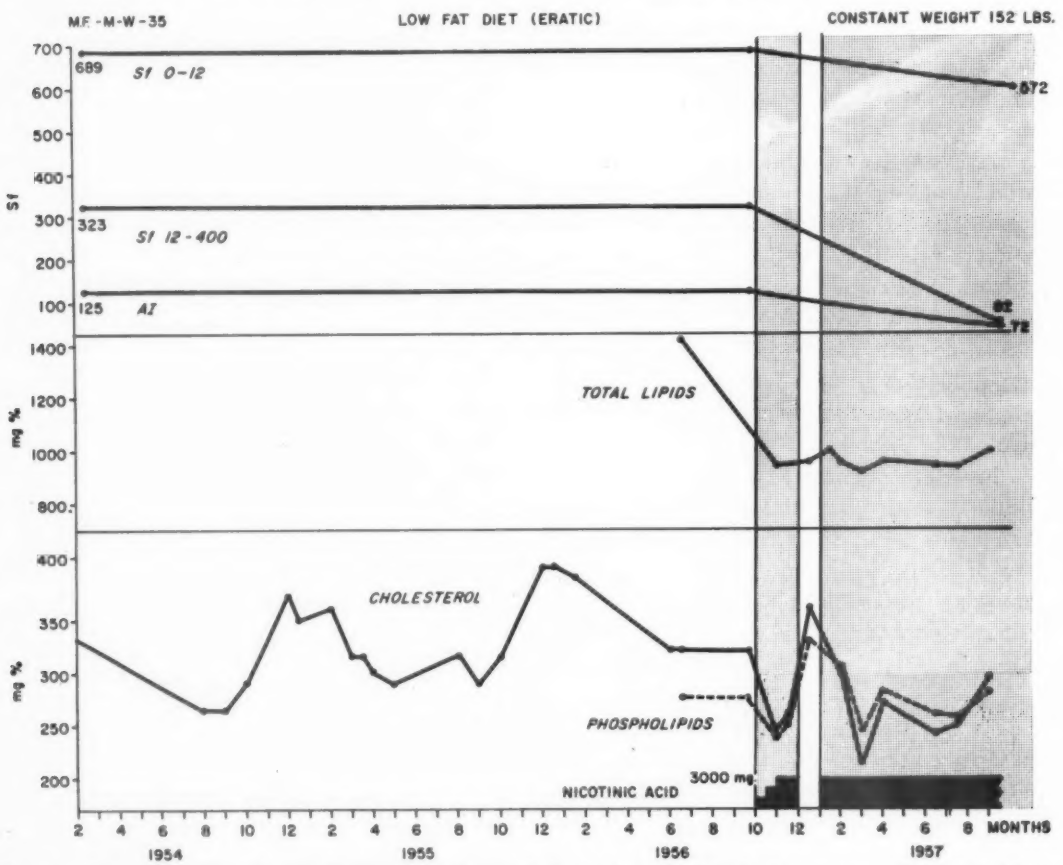

Fig. 1. Case of coronary heart disease with hypercholesterolemia. Marked response of blood lipids to nicotinic acid therapy.

that his body odor was stronger. Another patient developed hypothyroidism, the details of which will be given in a subsequent report.

Eight patients thought that they felt better with the nicotinic acid therapy than without it. Angina pectoris was decreased subjectively in seven cases. The liver function studies performed in most cases failed to show any significant change. Because of the adverse side effects, usually the flush and pruritis, the medication had to be discontinued in about one-third of the patients.

Effect on Blood Lipids: The blood lipid lowering effect of massive doses of oral nicotinic acid was confirmed in this study. In the presence of a pre-existing low fat diet there has been a further significant lowering of the blood lipids by the nicotinic acid. Figure 1 is a typical example of the response of the cholesterol level to nicotinic acid and Figure 2 shows a response

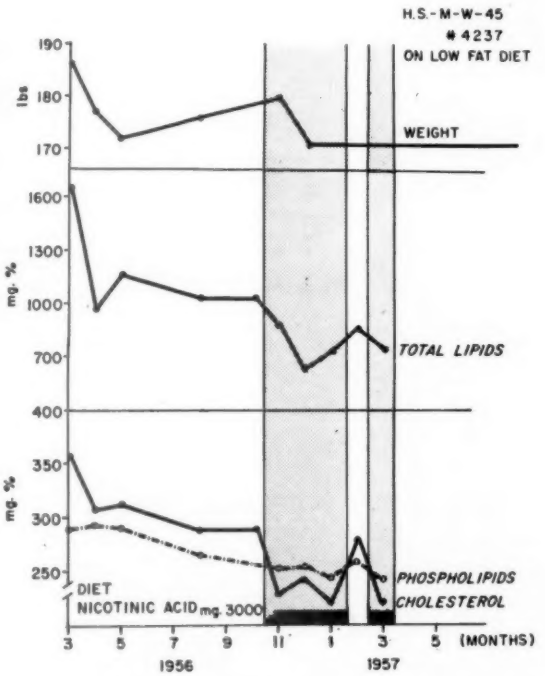

Fig. 2. Patient with coronary heart disease with a moderate drop of blood lipids on a low fat regime and a further dramatic decrease on nicotinic acid therapy.

to nicotinic acid even after a less significant response to diet therapy.

It was apparent to us that the dosage response varied from patient to patient. However, in general, the larger the dose the greater the percentage drop of the lipid concentration. This varied from 0 to 40 per cent. This difference in response might be explained by a combination of patient response dosage, and whether or not the drug was taken consistently.

Discussion

In our experience oral nicotinic acid therapy in large doses is the most effective method yet known to lower blood lipids. To the best of our knowledge this is desirable in those individuals who have high blood lipids and atherosclerosis. Other long term deleterious or beneficial effects on the body of large doses of nicotinic acid are unknown at this time but should be determined before this form of therapy is considered completely acceptable.

In our present experience the excessive production of undesirable side effects (Table I) precludes its use in about one-third of the candidates for lipid-lowering agents. A history of a peptic ulcer is a contraindication of its use in view of the possible reactivation of ulcer symptoms. It is hoped that the dramatic effectiveness of this agent in lowering blood lipids will lead to a better understanding of the whole problem of lipid metabolism and will improve our ability to prevent or decrease atherosclerosis.

Summary

(1) In our experience nicotinic acid given orally is probably the most effective method known to lower blood lipids.

(2) Many of its side effects are undesirable and may prevent its use in about one-third of the candidates for lipid lowering agents.

(3) No conclusions have been drawn concerning its effect on atherogenesis.

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Cardiac Infarction in the Bantu*

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In those areas of Africa in which reliable information is available, coronary thrombosis is reported to be uncommon in the Bantu.[1] In Cape Town the extreme rarity of this condition in the Bantu has previously been reported.[2] Thus in an analysis of the electrocardiograms of adult in-patients and out-patients attending Groote Schuur Hospital during 1953 and 1954, Vogelpoel and Schrire were able to find only two cases of myocardial infarction in the Bantu. The disease was found to be common on the other hand in the European population and less so in the Cape Coloured population.[2,3,4]

A more complete analysis of the five year incidence at this hospital during 1952–1956[4] has shown an incidence of infarction of only three cases in the Bantu as assessed by strict electrocardiographic criteria.[2] During the same period there were 760 cases in the European population diagnosed by the same criteria.

A similar low incidence of myocardial infarction in the Bantu population has been recognised in Johannesburg.[5–7] Thus Becker[5] in 1,487 necropsies on a predominantly Bantu people over the age of 30 attributed only one death to coronary thrombosis. Higginson and Pepler[6] in 523 necropsies found only eight patients in whom death could be attributed to coronary disease. They refer to a larger series of 1,328 consecutive necropsies (including their 523 cases) in which there were only seven cases of coronary thrombosis or myocardial infarction and one of ischaemic heart disease.

In Southern Rhodesia Gelfand[8] encountered no case of coronary heart disease in 1,500 consecutive admissions to his Bantu Hospital wards in 18 months. In Uganda the extreme rarity of coronary thrombosis in Negroes has been repeatedly affirmed by Davies and Williams[9,10] who have never seen a case of cardiac infarction in an East African which has been confirmed at autopsy. There has been only one case of proven coronary thrombosis in an African in their records since 1931. A similarly low incidence of myocardial infarction in the West African Negro has been reported by Edington.[11]

It is the purpose of this article to describe the three cases of cardiac infarction in the Bantu from this hospital that have come to autopsy during the period 1952–1957 inclusive.

Material and Methods

The electrocardiographic service of the Cardiac Clinic, during the period under survey, included all in-patients and out-patients attending Groote Schuur Hospital and the 44 in-patient teaching beds of the New Somerset Hospital. The former hospital has 854 beds and approximately the same number of Europeans attend both as out-patients and as in-patients as do non-European. The latter hospital is for non-Europeans only. The Bantu form approximately one-sixth of the total number of non-Europeans attending. Patients of all races are seen by the same physicians and there are equal facilities for electrocardiographic investigations and admissions.

The extreme rarity of cardiac infarction in the Bantu, as shown by our figures, reflects the uncommon incidence of the disease in this racial group. It is not due to any selection of patient population.

Similarly in the Pathology Department routine autopsies are done on all races, and whereas only 8 per cent (130,227 of 1,519,285) of the hospital attendances over a five-year

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period were Bantu, 11.4 per cent of the autopsies (188 of 1,641 over the age of ten) were in this racial group. Thus, as the autopsy rate is proportionately higher in the Bantu than in all other races, the rarity of the condition again cannot be attributed to a selection of material.

The patient population of Groote Schuur Hospital is selected because a means test prevents the admission of all but the poorest section of the community, and hence the incidence of coronary disease in the European is underestimated.[3] Almost all the non-Europeans are eligible, and this certainly applies to the Bantu. However, the number of Bantu in the Cape is far smaller than of the Coloureds and Europeans in the proportion of 67,800:351,100:280,800 (Bureau of Census and Statistics for March 1957).

Myocardial infarction is almost always associated with coronary atheroma and presents the same manifestations in the Cape Coloured as in the European. The same does not apply to the Bantu. The pathogenesis of the infarction differs in each of the three Bantu cases to be described.

Case Histories

Case 1. M. M., a Bantu male, age about 40 years, was admitted on April 27, 1953, with the story that three months prior to admission, while running for a bus, he suddenly experienced a raw central chest pain, radiating through to the back. He had to stop in his tracks and sat down on the pavement for about 15 minutes before the pain subsided. From that time on he felt the pain whenever he exerted himself. His effort tolerance became progressively diminished by the pain which was related only to effort.

Four days before admission, while standing at a bus stop, the pain became very severe, and was associated with acute dyspnoea and anguor animi. He collapsed and lost consciousness. When he recovered he found that he had been taken to his home. The pain persisted for two days, until admission.

The patient had lived in Cape Town for 20 years, had a good position as a garage attendant, with a fairly substantial income, and had adapted himself and his family well to the European mode of life, including a normal European diet.

On examination, apart from obesity, there were no abnormal physical findings. The blood pressure was 120/80. The electrocardiogram (Fig. 1) showed right bundle branch block, with S-T segment elevation, and serial changes indicative of recent infarction. On fluoroscopy the heart size was normal, but there was impaired pulsation high up on the left border of the left ventricle. The blood cholesterol was 167 mg %.

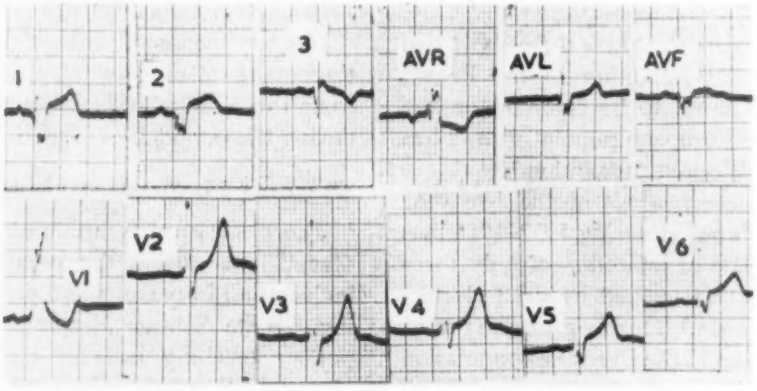

Fig. 1. The tracing shows the pattern of right bundle branch block. ST segment elevation is present in the left precordial leads, lead 1 and aVL, reflecting changes over the anterolateral aspects of the left ventricle. There were serial changes in these leads in subsequent electrocardiograms.

The patient was put on anticoagulants and treated in bed in the usual manner for cardiac infarction. During his stay in the hospital he was troubled by a considerable amount of pain, but at the time of discharge on June 8, 1943 he felt fit and reasonably well.

On Aug. 12, 1953 he walked into a police station, complaining of an uncomfortable feeling; here he rested for half an hour, after which he walked down the street where he dropped dead.

Autopsy Findings: At the Government medico-legal laboratory, the heart was found to be moderately enlarged. There was an old infarction involving the apex and the posterior aspects of the left ventricle and extending towards the septum; the circumflex branch of the left coronary artery was obstructed by a large clot which had retracted. There was also obstruction of the ante-

rior descending branch of the left coronary artery. Coronary atheroma was present to a degree which is commonly found in the heart of a European at autopsy.

Comment: This is a case of cardiac infarction in a young Bantu male associated with a typical history of angina pectoris and culminating in cardiac infarction from which he made a reasonable recovery. A subsequent coronary thrombosis resulted in sudden death. At autopsy, cardiac infarction was found in association with coronary thrombosis and diffuse coronary atherosclerosis no different from that found in the European population in Cape Town and elsewhere.

Case 2. S. B., a Bantu male, age 45 years, was first admitted on Nov. 2, 1954, with the story that for 14 years he had been subject to attacks of rhinitis and of asthma which had all the features associated with an allergic state. For a year and a half prior to admission the attacks had increased in frequency and severity, so that he required a course of ACTH to control his asthma.

In the intervals between his attacks of paroxysmal dyspnoea he became aware of moderate effort dyspnoea. For some time however, he was not quite certain precisely how long, he had been aware of pain in the left parasternal region, radiating up to the shoulder, strictly associated with effort and subsiding with rest. Three weeks before admission his condition deteriorated and he suffered from an attack of pain lasting all night. An electrocardiogram at that time showed T wave inversion in leads 1 and 2 with deep inversion from V_2 to V_6. He was found to be hypertensive with a blood pressure of 200/140, and subsequently was admitted to hospital.

The patient was a herbalist with ample financial means, lived a virtually sedentary life, with an adequate daily diet of meat and milk. His standard of living was that of an average European.

On examination he was extremely obese and the blood pressure was persistently elevated to the neighbourhood of 200/140. There was clinical evidence of left ventricular enlargement, and a presystolic triple rhythm was present. The electrocardiogram showed left ventricular hypertrophy (Fig. 2) and serial changes were present indicating superimposed ischaemia.

The blood urea and the van den Bergh reaction were within normal limits and the serum cholesterol was 210 mg %. A muscle biopsy showed no abnormal features. The patient was treated for three weeks in the hospital and was relatively well when discharged.

On September 23, 1957, he reported back to the Cardiac Clinic with a story that since his discharge he had retired and given up active work. During this time he had suffered from central chest pain on effort, burning in nature, radiating to the shoulder and jaw and relieved by rest. His asthma had improved, as had his dyspnoea. He was still living on a full diet.

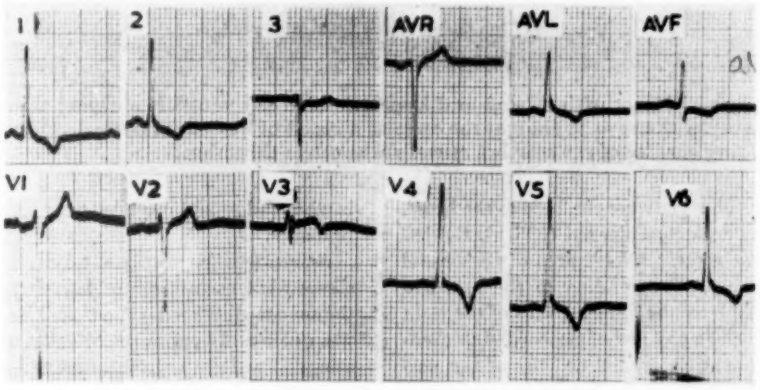

Fig. 2. The tracing shows the pattern of left ventricular hypertrophy. In subsequent records transient changes in the ST-T segments suggested superimposed ischaemia.

On examination the apex beat was left ventricular in type in the 5th space in the anterior axillary line, and a triple rhythm was still present. The blood pressure was 240/170, with 10 mm of alternans. Admission was advised for treatment of the hypertension. Six days later he was admitted with dysphasia and a right-sided hemiplegia.

The neurologic disturbances were those associated with a left cerebral lesion. The cardiovascular signs were essentially unchanged, and the blood pressure was 200/150. The electrocardiogram showed left ventricular hypertrophy (Fig. 2). The patient died in coma four days after admission.

Autopsy Findings: The autopsy was performed 48 hours after death. The body was that of a well-nourished, well-built, middle-aged Bantu male. Except for recent cerebral haemorrhage in the region of the left internal capsule which was the immediate cause of

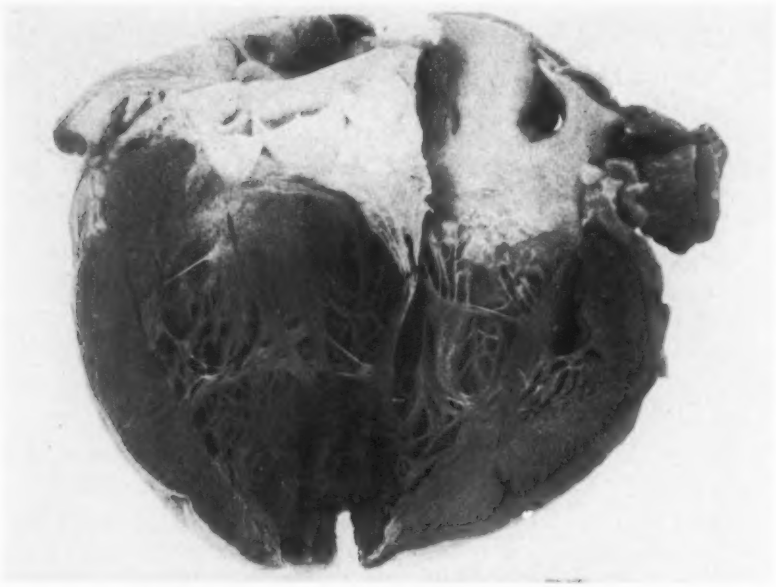

Fig. 3. Heart with dilated and hypertrophied left ventricle showing thinning of the myocardium at the apex as a result of healed infarction. Overlying surface of the scar is a mural antemortem thrombus.

death, the significant changes were confined to the heart.

The heart was moderately enlarged (557 g), the left side more so than the right. A focal area of pericardial opacity and thickening corresponding to the so-called milk spot was present over the anterior wall of the right ventricle and there were small foci of pericardial thickening overlying prominent superficial radicles of the posterior coronary artery in the right auricle. In neither of these lesions were adhesions between apposing pericardial surfaces apparent. Except for the mitral valve, which appeared slightly dilated (three fingers), the valves were competent and their cusps normal. Left ventricular hypertrophy and dilatation were striking (thickness 2.5 cm); the right ventricle was also hypertrophied but to a proportionately lesser degree (thickness 0.8 cm); both auricles appeared dilated, the left more so than the right. The myocardium appeared pale and firm except at the apex of the left ventricle, where the anterior wall and the anterior portion of the interventricular septum were replaced by firm fibrous tissue which extended from the apex proximally for 2 to 3 cm and resulted in appreciable thinning of the ventricular wall. This focus of fibrosis had the gross appearance of a healed infarct and on the endocardial surface was a layer of recent adherent antemortem thrombus (Fig. 3). The remainder of the endocardium was not thickened and showed only a few small subendocardial haemorrhages over the posterior wall. The coronary vessels were virtually free of atheroma and showed neither stenosis nor evidence of recent or old thrombosis.

The aorta showed a minimal degree of atheroma, which appeared in the thoracic portion as occasional discrete plaques free of ulceration or calcification, and in the abdominal portion only at the ostia of major branches.

Microscopically, sections taken from the left apex showed extensive areas of fibrosis completely replacing the myocardial fibres (Fig. 4). The fibrous tissue which was dense and hyaline resembled scar tissue of some duration. Partially organised antemortem thrombus was present on the endocardial surface and blended imperceptibly with the myocardial fibrosis. The coronary vessels in this region and elsewhere showed insignificant fibrous intimal thickening, but in none of those sectioned was there evidence of occlusion or old antemortem thrombus.

There was focal fibrous pericardial thickening over the vessels in the wall of the right auricle. As this fibrosis was acellular and did not in any way resemble that which follows organisation of an exudate, it may have been due to the persistent trauma of cardiac contraction to exposed and prominent coronary vessels. The fibres of the rest of the myocardium were hypertrophied and there was minimal increase of interstitial connective tissue.

The only other microscopic changes worthy of comment were those of malignant nephrosclerosis.

Comment: This is a case of severe hypertensive heart disease with angina pectoris and cardiac infarction in a well nourished Bantu male. The hypertension terminated in the malignant phase and death resulted from cerebral haemorrhage. At autopsy, the hypertrophied heart showed an old infarction involving the apex of

the left ventricle. The feature of the case was the almost complete absence of atheroma or other coronary disease. The old infarction was

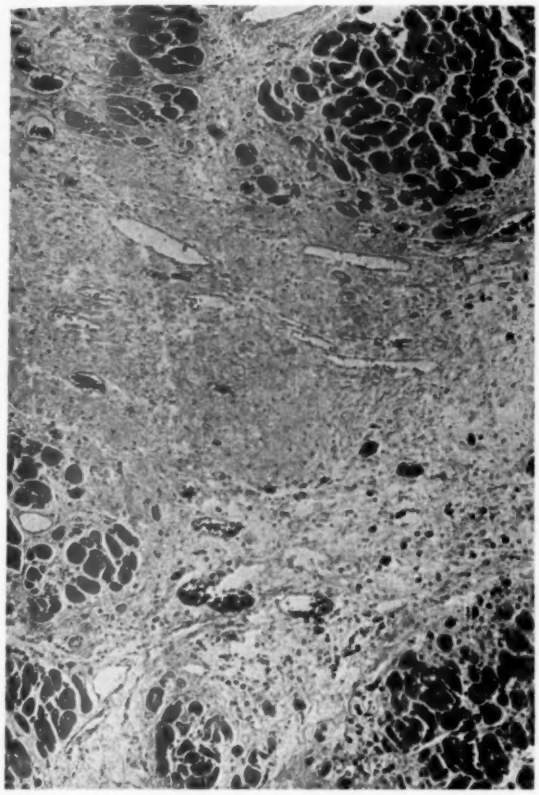

Fig. 4. In areas of old infarction, large portions of myocardium are replaced by vascularized, dense connective tissue. The absence of inflammatory signs indicates that the fibrosis is of some duration (haematoxylin and eosin X112).

attributed to coronary insufficiency, the arteries being unable to cope with the increased demands of the hypertrophied muscles.

CASE 3. S. N., a Bantu male, age 39 years, was admitted on April 3, 1956 with the story of cough and progressive effort dyspnoea for seven months. A month prior to admission he became orthopnoeic and had frequent attacks of paroxysmal dyspnoea, associated occasionally with haemoptyses. Both the cough and the dyspnoea started suddenly. Oedema of the legs was noticed a month after the onset of the dyspnoea and this soon spread to involve the abdomen, scrotum and arms. This was followed by abdominal pain, distention, diarrhoea, and frequency. At no time did he have any chest pain. His nutritional background was that of the average Bantu labourer in Cape Town.[12]

Gross oedema was present involving his legs, back, scrotum, penis, forearms and peritoneal cavity (ascites). He was orthopnoeic with bilateral basal effusions and lung congestion. His pulse was collapsing with a blood pressure of 140/30 and had a slight bisferriens quality;[13] the jugular venous pressure was raised to 16 cm and the liver was enlarged to 2 fingers' breadth below the costal margin. The cardiac apex was overfilled and left ventricular in type, in the 6th space in the anterior axillary line. There was a triple rhythm at all areas, with a loud basal systolic and early diastolic murmurs; at the apex a presystolic murmur and mid-diastolic murmur (Austin Flint) were present, in addition to the early diastolic murmur (confirmed on phonocardiography). The murmurs were attributed to advanced aortic regurgitation.

Slightly blood-stained pleural and peritoneal exudates were obtained on aspiration. The blood urea was elevated to 165 mg %. Slight jaundice was present, with a direct feeble prompt positive van der Bergh reaction and a serum bilirubin of 1.5 mg %. The Wasserman and Kahn reactions were positive.

The electrocardiogram (Fig. 5) showed low voltage and right ventricular dilatation; the only left ventricular surface lead was aVF, which showed T wave flattening. Radiological examination showed generalised enlargement of the left ventricle and aorta, with no disproportionate left auricular enlargement.

The patient was treated with digitalis, mercurials, aminophyllin, penicillin, salt restriction and repeated aspirations of the chest and abdomen, but despite inten-

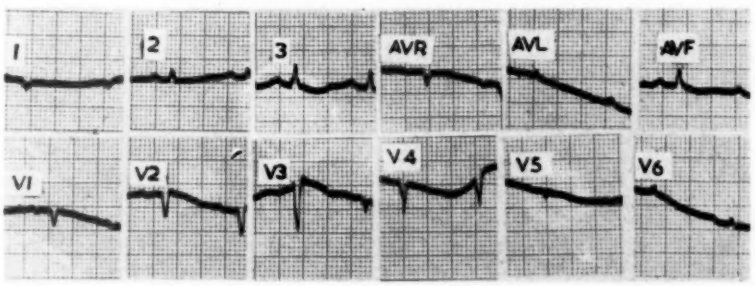

Fig. 5. The tracing shows low voltage and the positional changes associated with enlargement or dilatation of the right ventricle. Left ventricular "damage" is shown in the left-sided precordial leads.

sive therapy he failed to respond and died on April 19, 1956. Throughout his illness there was a disproportion between the severity of the aortic incompetence and the complete lack of response to vigorous treatment for heart failure, suggesting a myocardial factor as well as the mechanical effects of the valvular incompetence. Despite the character of the pulse and the murmurs, the condition was attributed to syphilis and not to rheumatic heart disease.

Autopsy Findings: The body was that of a well-built and well-nourished Bantu male. There was gross oedema of the legs and dependent parts and both pleural cavities contained straw-coloured effusions.

The heart was markedly enlarged (560 g) with both sides involved equally. Although the left ventricle appeared markedly dilated, its wall midway between the apex and the aortic cusps measured only 1.2 cm in thickness. The cusps of the aortic valves were thickened, their edges rolled and the commissures separated. The free margins of the cusps were retracted exposing the coronary ostia. These gross appearances were those of syphilitic valvulitis. The endocardium overlying the anterior wall of the left ventricle and the anterior portion of the interventricular septum was thickened and opaque, and here an area of 5 cm was largely replaced by scar tissue, thinning the ventricular wall. There was also extensive fibrosis of the mitral papillary muscles and the myocardium of the posterior left ventricular wall, well away from this lesion, also showed extensive patchy fibrosis. The mitral, pulmonary, and tricuspid valves were normal. Both auricles and the right ventricle (thickness 0.8 cm) were hypertrophied and dilated and, in addition, the right auricular appendage contained antemortem thrombus. The coronary vessels were dilated and entirely free of atheroma, their ostia were patent and there was no evidence of occlusion due to recent or old thrombus.

Along the entire length of the aorta there was evidence of extensive atheroma which was nonetheless superficial and presented only as discrete flattened plaques. Easily distinguished from this, involving the first 3 cm of the aorta, were raised greyish-pink plaques which resulted in puckering and scarring of the intimal surface. These foci macroscopically resembled syphilitic mesaortitis.

Although both lungs showed evidence of pulmonary artery embolisation, there was a recent infarct in the base of the right lung only. The other organs were not remarkable, apart from linear scars in the kidney resembling healed infarcts.

Histological sections of the myocardium, selected away from the area which showed the most pronounced gross fibrosis, revealed uniform hypertrophy of the muscle fibres. In places, groups of fibres appeared swollen and stained less intensely, due to an accumulation of glycogen in their cytoplasm. These alternated with areas where the muscle fibres were replaced by a focal increase of interstitial connective tissue. In the region of the most striking naked-eye lesion the muscle fibres had entirely disappeared and were replaced by vascularized, collagen-rich, dense connective tissue, which extended throughout

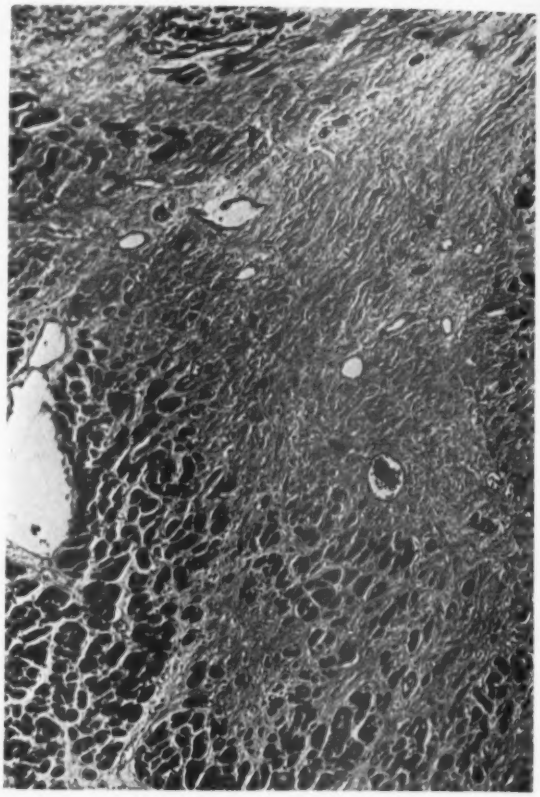

Fig. 6. Large area of fibrosis replacing muscle fibres indicates the presence of a healed infarct (haematoxylin and eosin X112).

the entire thickness of the ventricular wall (Fig. 6). The endocardium overlying this area was thickened, fibrous, and cellular and presented the appearances of organised thrombus. None of the vessels in the sections had their lumina in any way reduced. The right ventricle showed only myocardial hypertrophy and the appendage of the right auricle contained recent antemortem thrombus.

The focal fibrosis seen in most of the myocardium was of the type usually associated with prolonged ischaemia, due to progressive and gradually produced coronary insufficiency. Presumably this followed the death of individual fibres and was preceded by less severe ischaemic changes such as glycogen or fatty change, of which there was also evidence. However, in the anterior left ventricular wall and in the anterior portion of the interventricular septum, where fibrous tissue predominated almost to the exclusion of muscle fibres, the extent of the lesion was such that it must be labelled as a healed infarct. The presence of thrombus on the endocardial surface at this site is further support that such an acute lesion had indeed existed.

While some atheroma was present in the proximal aorta, the wall appeared thickened, largely as the result of cellular intimal hyperplasia and fibrosis. This taken in association with scarring of the media, perivascular

lymphocytic and plasma cell infiltration and endarteritis of the vasa vasorum is best accounted for on the basis of syphilitic mesaortitis.

The changes observed in the other organs were those associated with congestive cardiac failure, but the kidneys, in addition, showed vascular scars resembling healed infarcts.

Comment: This is a case of cardiac infarction in a Bantu associated with syphilitic aortitis but without coronary vascular disease, either ostial narrowing or atheroma, and not due to a myocardial gumma.

Discussion

These three cases are examples of cardiac infarction as encountered in the Bantu in Cape Town. The extreme rarity of this condition can be contrasted with its common occurrence in the European.[14,15]

Coronary Atheroma: In case 1, cardiac infarction occurred on the basis of coronary atheroma. This is the usual cause of cardiac infarction in the European.[16,19] The history, physical findings, electrocardiogram, and postmortem findings in no way differed from those observed in the European. In the Bantu, however, cardiac infarction on the basis of coronary atheroma is exceptional. In the Department of Pathology at Cape Town, during the period 1952–57, there were 119 cases of cardiac infarction at autopsy in Europeans and 43 in Cape Coloureds. The incidence of coronary atheroma was high in these groups and was associated with the infarction in almost every case. In the Bantu, however, the disease was extremely uncommon and atheroma when it occurred was less extensive and less severe than in the rest of the population. Apart from this case (which was autopsied elsewhere), there is no proven case of cardiac infarction due to atheroma in the Bantu in the records of the Pathology Department.

It may be argued that the dietary habits of this patient played a part in the production of his lesion as he was an urbanised Bantu, living for at least 20 years in good economic circumstances on a diet of European type. It has been suggested that a European diet, rich in fats (particularly of animal origin) is implicated in the pathogenesis of coronary atheroma as it is in the elevation of the blood cholesterol level.[20–29] A good review of this subject has recently been published by Brock and Gordon.[30] However, it is far more likely that some unknown factor, perhaps an individual metabolic defect, was responsible as his economic circumstances were by no means unique.[12]

Hypertension: The second case is an example of cardiac infarction in a severely hypertensive Bantu. The striking contrast between the coronary arteries of the Bantu and the European is again demonstrated. The association of hypertension and coronary atheroma is well known. In fact, the process of coronary atheroma may be accentuated by hypertension.[31–41] Although our patient suffered from severe essential hypertension for several years which subsequently developed into the malignant phase with termination in a cerebrovascular accident, his coronary arteries at autopsy were completely free of atheroma. This is all the more striking in view of the long story of angina pectoris both before and after an undoubted episode of myocardial infarction which was later confirmed at autopsy.

The finding of cardiac infarction in the presence of normal coronary arteries suggests that coronary flow was insufficient for an abnormally hypertrophied heart muscle. Although macroscopically and microscopically the coronary arteries appeared adequate, the coronary flow was in fact inadequate. "Coronary spasm" may be suggested as an explanation for a prolonged attack of coronary insufficiency leading to cardiac infarction but is hardly likely to apply to the regular occurrence of pain on effort.

The coronary arteries as a rule enlarge in hypertensive heart disease as the heart hypertrophies.[42–46] Harrison and Wood[46] suggested that the degree of the coronary enlargement keeps pace with the needs of the heart and that "relative ischaemia" is not a cause of cardiac failure in hypertension. They felt that the fibrosis occurring in the hearts of patients with hypertension, without appreciable coronary sclerosis, was due to "fibrous tissue hypertrophy" and not a result of muscle destruction. That cardiac infarction can occur in the absence of coronary occlusion has been established[47–56] and Harrison and Wood[46] were inclined to the view that this could be attributed to a diminution of coronary flow during a phase

of cardiac failure rather than to relatively small coronary arteries or spasm. In almost all of these cases, however, though actual coronary occlusion may have been absent, coronary atherosclerosis of varying degrees was present. Fishberg[57] states that in the past many clinicians including Allbutt[58] and Libman[59] believed that anginal pain in essential hypertension does not necessarily result from coronary arteriosclerosis, the pain being ascribed to cardiac strain or aortic disease. He himself, however, believes: "The occurrence of anginal pain in a hypertensive warrants the diagnosis of coronary arteriosclerosis," and in every instance of essential hypertension with definite anginal pain that he has examined at necropsy narrowing of the coronary arteries has been present. During certain critically adverse circulatory conditions such as haemorrhage, shock, sustained effort, tachycardia, and toxaemia, cardiac infarction may rarely occur in normal vessels,[55] though even under these circumstances some degree of coronary arteriosclerosis is present.

No such factors can be invoked in our case, nor was he ever in manifest heart failure. The presenting symptoms were angina pectoris followed by cardiac infarction, at a stage when he had no symptoms or signs of heart failure. Thus neither diminution of flow due to cardiac failure nor diminution of flow due to extracardiac circulatory factors can be the explanation. There is no evidence that the fact that he was an allergic subject and suffered from asthma played any part in the condition. Coronary insufficiency due to relatively small coronary arteries seems to be the most satisfactory explanation. The same postulate has recently been made for the myocardial fibrosis occurring in rheumatic mitral and aortic valve disease.[78]

Of interest is the fact that the whole vascular tree was not spared the effects of atheroma. In contrast to the normal coronary arteries were the atherosclerotic arteries at the base of the brain. Cerebral haemorrhage, presumably on the basis of an arteriosclerotic vessel, was in fact the terminal event. Atheroma is characteristically patchy in distribution and disproportionate involvement of the cerebral arteries is not uncommon. Arteriosclerosis including atherosclerosis are common in the Bantu[5] and cerebral thrombosis and haemorrhage based upon hypertensive atherosclerosis are not uncommon, but perhaps are less common than in the European.[1]

This patient, whose economic circumstances and standard of living were far better than the average Bantu, like case 1, lived for many years on a normal European diet. A rough assessment of his dietary intake indicated little difference from that of the average European. The freedom from coronary atheroma cannot lightly be attributed to an excessively low intake of fats, especially animal fats, so common in the Bantu, and the cause must at the moment be regarded as unknown.

Syphilis: The last case is one of syphilitic heart disease, where the pulse and heart murmurs closely mimicked those of rheumatic heart disease. However, this is not uncommon in luetic heart disease, and in the Bantu subject syphilis is a far commoner cause of aortic valve disease than it is in the European.[60] Of interest was the clinical observation that the heart failure was progressive, irreversible, and nonresponsive to treatment. The degree of aortic incompetence did not appear to be entirely responsible for the clinical picture, and a superadded myocardial factor was therefore suspected. At autopsy this was shown to be cardiac infarction. Endocardial thrombosis had been superimposed on the infarction and evidence of systemic emboli was present. No syphilitic ostial stenosis was present and the coronary arteries were free of disease including atheroma.

Syphilis is a well-known cause of coronary artery stenosis and occlusion. The incidence of severe narrowing or complete obstruction of the coronary ostia in syphilitic aortitis is from 15 to 25 per cent in the European[61,62] and anginal pain is common. Myocardial infarction, on the other hand, is rare. Burch and Winsor[63] reviewed the literature for the ten years preceding 1942 and found only six cases of cardiac infarction from syphilitic coronary stenosis. They added three of their own, all in Coloured patients. Love and Warner,[64] however, found four cases of acute infarction and eight of marked myocardial fibrosis in 15 cases with ostial stenosis. Jones and Bedford[62] found the

clinical syndrome of cardiac infarction in 10 of 103 cases and attributed this to coronary atheroma and thrombosis but without any pathological support. In Johannesburg, Jacobs and Elliott[65] in their series of cases of ventricular aneurysm found syphilis to be an important cause in the Bantu. The coronary arteries were normal in their series and the cause of aneurysm in their cases was attributed to coronary artery stenosis or actual gummatous infiltration of the myocardium. In the European with syphilitic heart disease, however, unlike the Bantu, atheroma is a frequent associated finding.[66–69]

In our case the striking absence of atheroma was a feature we have come to expect in the Bantu. However, the complete absence of coronary ostial narrowing or gummatous myocardial involvement is unexpected. Presumably the same factors were operative as in case 2, namely, an inadequate coronary flow through arteries supplying a hypertrophied heart. In this case, however, the added factor of reduced cardiac output associated with heart failure was probably also operative. The complete absence of pain too is worthy of mention.

Causes of Rarity of Cardiac Infarction in the Bantu: In conclusion, attention is again drawn to the rarity of cardiac infarction in the Bantu. Significant coronary atheroma is even more uncommon. Despite the presence of well-known aggravating factors such as severe hypertension or syphilitic aortitis coronary atheroma may be strikingly absent. The relative immunity of the Bantu is not understood. The presence of an extra coronary supply through an especially developed third primary division of the left coronary artery[70] has not been confirmed[71] nor is there evidence as yet that the coronary artery system of the Bantu is capable of a freer anastomosis between different branches than that of the European. Whether the Bantu has a lesser tendency to intravascular clotting is still under investigation[72] and adequate information is as yet absent. That intravascular coronary arterial thrombosis plays an important part in the production of atheroma,[19,73,74] is receiving more and more attention and the claim has been made[75] that the blood of patients with ischaemic heart disease is hypercoagulable.

Lastly, the rarity of atheroma in the Bantu has been associated with their low consumption of fat, particularly animal fat, in their diet.[1,21] That the two are causally related, however, is uncertain.[76,77] The only patient with coronary atheroma of our three cases of cardiac infarction consumed a normal European diet, but a similar diet was consumed by the second patient whose coronary arteries were completely free of atheroma. As the cause of atheroma is little understood, the relative freedom of the Bantu from atheroma is equally ill understood.

Summary

(1) Cardiac infarction in the Bantu is exceedingly rare. During the six-year period, 1952–57, only three cases of cardiac infarction were proven at autopsy at the department of pathology and in the Groote Schuur Hospital.

(2) Of these cases, only one was associated with extensive atheroma, the pathological findings being identical with those encountered in the European.

(3) One case was shown to be associated with severe hypertension but with no atheroma of the coronary vessels. The other occurred in the presence of syphilitic aortic incompetence and syphilitic aortitis but without any involvement of the coronary ostial or coronary vessels. The infarctions in these two cases were attributed to coronary insufficiency, due to an inadequate coronary supply to a greatly hypertrophied heart muscle.

(4) The rarity of atheroma in the Bantu is discussed, the cause of which is unknown.

Acknowledgments

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Myocardial Infarction in the Negro

Historical Survey as It Relates to Negroes*

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IN A 1927 SURVEY Stone and Vanzant[1] found arteriosclerotic heart disease four times as common in white as in Negro subjects. Schwab and Schulze[2] and Wood *et al.*[3] discovered a high incidence of organic heart disease as a whole in Negroes as compared with whites, but this they believed essentially due to a high incidence of hypertensive and luetic heart disease among Negroes. Laws[4] studied 645 cases admitted to his clinic and found organic heart disease in 4.9 per cent of all Negro and 3.3 per cent of all white admissions. Lisa and Ring[5] reported more than four times as many whites as Negroes in their series of 100 cases of myocardial infarction. In Gager and Dunn's[6] series there were twice as many whites as Negroes. Hedley[7] concluded that coronary arteriosclerosis and thrombosis are uncommon in Negroes. Johnston,[8] reporting an autopsy analysis of 400 patients above the age of 39, found the incidence of marked coronary sclerosis to be 24 per cent for white males, 9 per cent for Negro males, 10 per cent for white females, and 4 per cent for Negro females. He concluded that members of the white race are much more susceptible to coronary sclerosis than are Negroes.

Bean[9] was able to find only 16 cases of myocardial infarction in Negroes from among 300 cases examined at necropsy. Weiss[10] contended that coronary occlusion in the absence of hypertension was rare in Negroes, although he did note that the same was true of whites in his experience. Reporting on a series of 877 autopsied cases, Perry and Langsam[11] found coronary thrombosis to be four times as frequent in the white as in the Negro. These authors also state that coronary thrombosis without hypertension is relatively rare in Negroes but other vascular accidents, even in the absence of hypertension, are extremely common. They also concur with the others cited that hypertensive cardiovascular disease and luetic heart disease are very common in the Negro. Reporting from the Gallinger Municipal Hospital in Washington, D. C., Fitzgerald and Yater[12] found an identical number of Negroes and whites with coronary occlusion, but since twice as many Negroes were admitted to the hospital, the white to Negro ratio was 2:1. Prior to the monumental work of Yater and his co-workers,[13] the lowest white to Negro ratio of arteriosclerotic heart disease was reported by Holoubek[14] in 1946 whose figures on white and Negro patients dying of arteriosclerotic heart disease were 59 to 41, respectively. Thus, reviewing the literature relating to the incidence of coronary artery disease in Negroes, one finds great disparities in the figures, but in no series yet reported has the Negro incidence been higher than the white.

As interest in coronary artery disease grew and contributions to the literature became more prolific, there appeared a school of thought which maintained that the cardiovascular system of Negroes differed fundamentally from that of whites. Most articulate in the 1930's, this school seemed to propound the tenets that the cardiovascular apparatus of the Negro was defective;[15,17] that his nervous system was less highly organized;[16] that his nervous system was inherently dissimilar;[17] that the anginal syndrome was extremely rare in Negroes;[10,15–19] that, to be sure, there was a large incidence of

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heart disease in the Negro but this was preponderantly of the hypertensive and luetic varieties;[2,3] that arteriosclerotic heart disease and coronary occlusion were very infrequent in the Negro;[5,8,9,11,18] and when the latter did occur the typical pain so characteristic in the white race was absent in the Negro, either because he could not feel it,[16,17] or lacked the intelligence to describe it.[19] The cardinal symptom of coronary occlusion in the Negro was said to be dyspnea.[19]

One wonders why coronary arteriosclerosis, a clearly degenerative disease, should be so uncommon in the Negro if his cardiovascular system is defective; or what specific morphologic or functional differences exist between the white nervous system and the Negro nervous system. Such views, nevertheless, went long unchallenged, since sufficiently large segments of the Negro population were not studied and reported from regions other than the Southeastern United States.

We consider the doctrine to be false that Negroes, being inherently inferior, do not feel the pain of angina pectoris or acute myocardial infarction as do white patients. Nevertheless it has been loudly expounded. In 1928 Davison and Thoroughman,[15] analyzing 257 cases of heart disease admitted to the Colored Division of Emory University, deplored the difficulty with which they were able to obtain an accurate history from the Negro patient, a "type of individual . . . who complains very little and who notices his symptoms very little, unless they are of sufficient degree to cause complete or partial disability." Their colleagues who discussed this paper, C. T. Stone and James E. Paullin, were in complete accord on the rarity of anginal pain in the Negro. The former could not recall a single instance but the latter did concede that he saw one case. Stone was of the opinion that "the Negro has probably inherited a defective cardiovascular apparatus which begins to break down sooner than that of the (white) man." He, however, did not explain why this defective apparatus did not break down under the ravages of coronary sclerosis. In 1931 Roberts,[16] observing that the anginal syndrome was rare among Negroes, explained it by the hypothesis that Negroes have a less acute perception of pain since they "seem to be less highly organized nervously." He further opined that the Negro lacks stress and does not worry very much since the "average Negro never takes anything very seriously for very long." Schwab and Schulze[17] postulated that inasmuch as heart disease in the Negro as compared with the white race is of greater incidence, occurs at a younger age, pursues a more rapid course and has a higher mortality rate, the cardiovascular system of the American Negro of the South is inferior to that of the white race and is more vulnerable to insult. This could be in the form of infection, degeneration, or toxemia, or the stress and strain incident to the complexities and modes of modern occidental civilization. Going further, these authors felt that "certainly there is a profound dissimilarity in the psyche and sensorium of the two races under consideration," and an "inherent dissimilarity in the nervous system of both races." The authors, nevertheless, failed to explain why the Negro of the South was different from the Negro of the North.

Toward the end of the 1930's there was some mitigation of the attitude that the Negro could not feel pain but rather that he was not sufficiently intelligent to describe it. Weiss,[45] noting that the angina incidence was low in both the Negro and white patients without hypertension, speculated that "a lack of ability to fully describe and interpret the sensation of cardiac pain can explain its rarity in the Negro charity as compared with the private white patient," since "more than moronic intelligence" was considered required to describe coronary pain. Burch and Voorhies[18] agreed that there was a low incidence of coronary occlusion and angina pectoris in the Negro as compared with the white, the ratios being 7:2 and 4:1, respectively. The authors reflected that the relatively low incidence of angina pectoris in Negroes could be due to the lack of intellectual ability to interpret fully and describe the sensation of pain; to the distress of myocardial, cerebral, or renal failure symptoms which often obscure all history of angina pectoris; and because an uncomplicated anginal type of heart failure usually occurs in an ambulatory patient. Although here is the tacit admission that Negroes with coronary artery disease simply may not be hospitalized as

often as whites, the authors nevertheless felt impelled to conclude that there is probably a genuine difference in racial incidence. In the same vein Weiss[10] states that "most clinicians in the Southern part of the United States are in accord that angina pectoris is infrequently encountered in the Negro." Here again one wonders why geography should make such a difference.

Dealing more specifically with coronary occlusion in the Negro, Hunter[19] found that coronary occlusion is rarely diagnosed before death in the Negro since Negroes rarely have pain but suffer from dyspnea as the outstanding symptom of this catastrophe. In his series the almost invariable picture was an exacerbation, usually sudden, of a decompensation of several years' duration. Therefore, he believes, a careful clinical and electrocardiographic examination of Negroes with acute left ventricular failure will yield many diagnoses of coronary occlusion. In contrast, he found that over one-half of his white patients had pain. Accepting the rarity of angina pectoris in the Negro as axiomatic, the author attributes the purported high rate of painless coronary occlusions in Negroes to the dilatation of collateral coronary vessels secondary to hypertension of long duration, which he believes to be common in Negroes and to occur 10 to 15 years earlier in the average Negro than in the average white cardiac patient. Otherwise he could find no significant difference in the clinical signs of myocardial infarction in the two racial groups nor any difference in incidence when comparing indigent Negroes and indigent whites under the age of 70 years.

It remained for the magnificent paper of Yater *et al.*[13] to explode the myth of racial difference between Negroes and whites as far as coronary artery disease is concerned. Unfortunately, the patients in this series were confined to male army personnel between the ages of 18 and 39 and therefore limited in age range and sex. However, certain conclusions reached in this work completely controvert previous notions about coronary artery disease in Negroes. In an exhaustive, thoroughly controlled, and excellently documented analysis, these authors found the incidence of coronary artery disease among Negroes to be somewhat more than two-thirds that of white soldiers, or a white to Negro ratio of about 3:2. Further analysis of their statistics on Negroes showed that of 63 cases 26 died and 37 survived. The fatality rate in Negroes was 41 per cent as compared with 55 per cent for whites. The average age of attack was 31.9 years. Of those who died only six patients had any history of previous heart disease and only 14 men (54 per cent) gave a history of precordial pain, the remainder showing symptoms of nausea, vomiting, dyspnea, and congestive failure. Of the survivors, however, 92 per cent experienced pain. Other coexisting symptoms of the acute attack were dyspnea, weakness, sweating, vomiting, and dizziness, just as in white soldiers. Physical examination yielded identical findings in both races. The height-weight relationship of the Negro soldiers was the same as for the group as a whole, and the history relative to the previous existence of heart disease revealed the same trend as in the whites. The electrocardiograms showed 15 anterior, 14 posterior, 2 posterolateral, 1 lateral, and 5 unlocalized infarcts.

On the basis of their data these authors take exception to Hunter's[19] thesis that the symptomatology of coronary artery occlusion in Negroes is different from that in Caucasians, at least in men under 40 years of age. They also conclude that, if one is to judge from the literature, Negroes with acute coronary artery occlusion are rarely hospitalized in life. We fully endorse this view. Probably of great import, but still inexplicable, are the findings of Blache and Handler[20] that the rate of coronary artery degeneration in the Negro lags about one decade behind that of the white. Whatever the explanation may eventually be, the mere observation that the coronary tree in Negroes withstands degenerative changes longer, conclusively refutes the defective cardiovascular theory of the earlier writers.

Data from the Harlem Hospital

Because there is still a deplorable paucity of reports in the literature on coronary artery disease and acute myocardial infarction in the Negro, we felt impelled to analyze our statistics at the Harlem Hospital in New York City. Harlem Hospital is located in one of the largest

Negro urban communities in the world. Although compared with the city as a whole this is still an underprivileged community, the peculiar economic and sociologic factors operative in the southeastern United States are less intense. We believe, therefore, that our milieu bears a fair degree of resemblance to any white urban community in the Northern United States of comparable economic status.

During the five-year period from 1950 to 1954, inclusive, there were 312 cases of myocardial infarction diagnosed clinically. Of these, 160 cases were excluded from this study because of insufficient corroborative data, tracings which were not typical, very rapid demise following admission or departure from the hospital against advice, and medicolegal cases. Of the remaining 152 cases, 21 were white and therefore excluded except for studies of racial comparisons. Our reportable series therefore consists of 131 cases, all Negroes with proven acute myocardial infarction. We selected the five-year period indicated above rather than some other because it marked the gradual transition of routine electrocardiography at the Harlem Hospital from the 4-lead to the full 12-lead electrocardiogram.

Table I shows the total number of admissions to the Harlem Hospital and number of myocardial infarcts analyzed racially. It is seen that whites comprise 5.8 per cent of the admissions, but contributed 13.1 per cent to the total number of myocardial infarctions. The white to Negro ratio is therefore 2:1, if one is to judge from the prima facie evidence.

In spite of the figures contained in Table I we believe this ratio to be misleading. Although the Harlem Hospital is situated in a predominantly Negro community, it is also a municipal hospital and its district is traversed by two main subway trunks and at least six main bus lines. Passengers stricken in passage while on vehicles of public transportation are taken to the Harlem Hospital by ambulance, as are those whites who operate small businesses in Harlem and collapse in their stores. In this sense the hospital is drawing from a much wider area than its immediate community but getting only the most desperately ill whites from this greater area. Approximately half of the whites in this series fall into these categories. The corrected ratio, therefore, if these whites were excluded, would be closer to 1:1.

TABLE I

Number of Admissions and Proven Cases of Myocardial Infarction (1950–54)

Number	Negroes	Whites	Orientals	Percentage of whites
Total admissions				
111,323	104,506	6,818	0	5.8
Myocardial infarction				
152	131	20	1	13.1

Relative to the sex incidence, Table II shows that 52.3 per cent of the admissions to the medical wards were males. In the infarction series 56.1 per cent were males in the Negro group and 63.7 per cent were males in the white group of 20 cases. The conclusion is therefore tenable that there is no significant racial difference in the sex incidence. Comparison of death rates, overall, and for Negroes alone (Table III), again shows no statistical difference between the two races.

TABLE II

Myocardial Infarction Analyzed by Sex

	Number	Males	Females	Percentage of males
Total admissions to medical service	31,463	16,471	14,992	52.3
Myocardial infarction				
Negro	131	72	59	56.1
White	20	13	7	63.7

All subsequent analyses are confined to the Negro members of this series in conformity with the title of this article. It is myocardial infarction in the Negro that we are primarily concerned with in order to compare whatever

statistics we obtained with the classic figures accepted for the human race as a whole, at least in the United States. We will present data from

TABLE III

Over-all and Negro Mortality Rate (1950–54)

	Number	Fatal Cases	Mortality rate	Percentage male deaths	Percentage female deaths
Total series	152	68	44.7	21.0	23.7
Negroes	131	61	46.5	21.4	25.1
Whites	20	7	35.0	—	—

the viewpoints of predisposition, precordial pain during the acute attack, age, location of infarct, seasonal incidence, and life duration in fatal attacks.

PREDISPOSING FACTORS

Hypertension: The more serious established predisposing factors in myocardial infarction are hypertension and diabetes mellitus. Yater *et al.*[13] found the relative incidence of coronary artery disease to be more than twice as high in those soldiers with systolic pressures of 140–169 mm Hg than in those with pressures of 100–139 mm Hg. Moreover, there were four times as many deaths in those inductees with diastolic pressures of more than 89 mm Hg at the time of induction than in those with diastolic pressures of less than 90 mm Hg. In a series of 145 patients, Levine and Brown[21] found that 40 per cent had had pressures of 160/100 or more before the acute attack and many apparent normotensives had evidence of hypertensive disease in the ocular fundi. A total of 33.9 per cent in Conner's[22] series of 274 cases had hypertension, with the highest incidence in the age group of 56 to 60 years of age. Of Palmer's[23] 212 cases, an average of 75 per cent had hypertension, the mean blood pressure value before the attack being 170/100. Analyzed by age, hypertension existed in only 37 per cent of patients below the fifth decade of life but in 78 to 84 per cent of patients in subsequent decades up to the eighth. Gross and Engelberg[24] found the incidence of hypertension to be 90 per cent in a series of 100 cases.

Weiss[10] noted that in his autopsy experience the incidence of coronary occlusion in the absence of hypertension was rare in the Negro and uncommon in the white patient. In a subsequent work confined to a study of the Negro race Weiss and Gray[25] reaffirmed the part that myocardial infarction in the Negro was infrequent in the absence of hypertension. In their series, 87.5 per cent of the males who had sustained a myocardial infarction had had hypertension. Master and co-workers[26] observed that hypertension antedated coronary occlusion in 69 per cent of 538 patients. Hypertension was less frequent in those patients who were suffering from the initial attack than in victims of multiple attacks.

While it seems evident that patients with hypertension are more prone to coronary atherosclerosis than those without hypertension, and this difference is most striking in the first five decades of life, the causal relationship between the two still remains an enigma. It is not clear why Negroes, with a higher incidence of hypertension, do not have a correspondingly higher incidence of coronary atherosclerosis, but in fact resist such changes according to the work of Blache and Handler.[20] Nor is it clear, as Davis and Klainer[27] point out, why men without hypertension have much more coronary artery disease than women without hypertension nor, in fact, why the degree of coronary atherosclerosis in women remains significantly lower in spite of a higher incidence of hypertension in this sex. In another work the same authors[28] offer evidence that although the incidence of coronary atherosclerosis in patients with essential hypertension is relatively high, hypertension *per se* is not the cause of this higher incidence. The conclusion is reached that the two diseases are probably the independent results of a common etiologic factor, whatever that may be. The belief that hypertension is not the primary factor in the development of coronary atherosclerosis is also voiced by White, Edwards, and Dry.[29]

It is easier to understand the possible compensatory mechanism for increased myocardial irrigation which hypertension may represent following an attack of acute coronary occlusion.

Yater *et al.*[13] noted that the blood pressures of those of their patients who survived were slightly higher than of those who died. The authors postulate that this may indicate a better adjustment by the survivors to a diminished myocardial blood flow. Palmer[23] in his follow-up studies, observed that 50 per cent of the patients in his series developed hypertension within one year of the acute attack and a yearly increment was noted thereafter until the figure finally reached 72 per cent. The observation of Master *et al.*[26] that patients suffering subsequent attacks of myocardial infarction tended to have higher blood pressures than those with initial attacks also follows the general pattern.

Diabetes: Linked to the problem of hypertension is that of diabetes mellitus. The disastrous effects of this disease on the coronary vessels through the mechanism of accelerated sclerosis is a theorem of medicine. Robinson[30] notes that 20 per cent of all cases of coronary thrombosis are diabetics, and that diabetics are 14 times as prone to develop acute coronary thrombosis as nondiabetics. The view expressed by Bradley and Bryfogle[31] and unqualifiedly accepted by us, is that the diabetic patient with an acute myocardial infarction automatically has a prognosis similar to that of the "poor risk" patient from the general nondiabetic population. A curiosity often observed but never understood is the peculiar reversal of sex incidence of acute myocardial infarction in the presence of diabetes mellitus, especially after the fifth decade.

Incidence of Predisposing Factors: In our analysis we have classified our patients according to whether they did or did not have predisposing diseases. The predisposing diseases are hypertension, diabetes, lues, rheumatic heart disease, and senility (the criteria being 75 years or over). The data are very enlightening. As seen in Table IV, cases with predisposing disease accounted for 71.1 per cent of the total number of cases, of which 38.2 per cent were fatal and 32.9 per cent nonfatal. Cases without predisposition accounted for only 28.9 per cent of the total, of which 8.4 per cent were fatal and 20.5 per cent nonfatal. In the cases with predisposition the ratio of nonfatal to fatal cases is therefore approximately 1:1, whereas in cases without predisposition the ratio is roughly 2.5:1. Analyzing the fatal cases, it is noted that the predisposition to nonpredisposition ratio is approximately 4.5:1. It is clear, therefore, that the chances of survival following an episode of acute myocardial infarction in the Negro, as in the population as a whole, are strongly contingent on the presence or absence of predisposing factors.

PAIN IN MYOCARDIAL INFARCTION

As stated elsewhere in this paper, statements have been abundant in the literature that anginal pain is rare in the Negro, and that in acute coronary occlusion dyspnea is the usual substitution symptom. That a painless myocardial infarction may be sustained by anyone, or that pain and dyspnea may coexist to a varying degree are facts of common medical knowledge. Yater *et al.*[13] observed gross myocardial infarcts in 13 per cent of their patients who died suddenly without any previous history. Reporting on 255 cases verified by autopsy, Landman, Anhalt, and Angrist[32] found 28 cases, or 12 per cent of the total, which had had no history of symptoms of any antecedent cardiac disease. Rakov[33] gives the incidence of painless infarction as ranging from 5 to 20 per cent.

Dyspnea as a coexistent or substitution symptom in myocardial infarction is well known. Obrastzow and Straschesko[34] described it as status dyspnoeticus in their classic report. Wolff and White[35] observed it in almost all of their 23 cases. Hamman[36] asserted that it was rarely absent. Rosenbaum and Levine[37] found dyspnea in 71 per cent of their 208 cases.

TABLE IV

Incidence of Predisposing Factors in Negroes

	Fatal cases	Nonfatal cases	Total
With predisposing factors	50 (38.2%)	43 (32.9%)	93 (71.1%)
Without predisposing factors	11 (8.4%)	27 (20.5%)	38 (28.9%)
Total	61	70	131

Bean[38] noted dyspnea in 95 per cent of his cases. Phipps[39] described a symptom complex consisting of dyspnea, palpitation, and precordial discomfort or pain. Endless numbers of case reports could be cited to show the prominence of dyspnea as a cardinal symptom of acute myocardial infarction and its coexistence and coalescence with unequivocal precordial pain. We are not asserting that it does not exist in the Negro. We are merely controverting on the basis of our experience, that it exists in the Negro to the obligatory exclusion of frank precordial pain.

As noted in Table V, pain occurred as an admission symptom in 74.0 per cent of the cases. Of those patients who were admitted in a state of shock and beyond the reach of medical interrogation, 18 patients or 13.7 per cent of the total series later admitted that they had had precordial pain prior to their collapse. Thus, a total of 87.7 per cent of the patients had precordial pain as one of their main symptoms. This compares very closely with the observation of Yater *et al.*[13] who noted precordial pain in 92 per cent of their Negro patients, but is in marked conflict with the findings of Hunter[19] already cited. In our series most of the patients complained of radiation of the pain to the neck, back, either or both shoulders, and/or either or both arms. The pain was variously described as crushing, tearing, heavy, squeezing, and grabbing. The presence or absence of pain apparently had no bearing on mortality. Of the fatal cases, 88.5 per cent had pain, and of the nonfatal cases 87.1 per cent. This is certainly not statistically significant.

TABLE V

Incidence of Pain in Myocardial Infarction in the Negro (1950–54)

	Male	Female	Total (%)
Pain present	53	44	97 (74.0)
Pain and collapse	9	9	18 (13.7)
Total cases with pain	62	53	115 (87.7)
No pain	10	6	16 (12.3)

CONSIDERATION OF AGE

The progressively lower age groups into which the relentless hand of myocardial infarction is reaching has been the cause of ever increasing if helpless alarm. Thus, in our series the youngest victims were in their third decade (Fig 1).

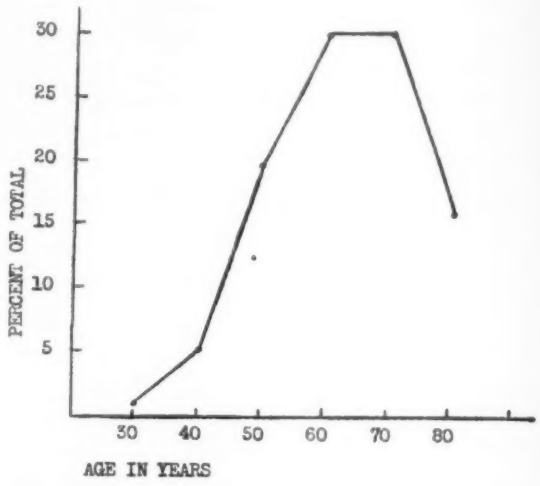

Fig. 1. Age incidence of myocardial infarction in the Negro.

To be sure, numerous younger victims, verified by autopsy, have been described in the literature. However, such cases are still considered rare enough to warrant individual reports in the literature, as MacDougall's[40] report of fatal coronary occlusion in a 16-year-old girl.

The patients in our series show a sharp rise in incidence in the fifth decade and a greater rise in the sixth decade; a plateau continues in the seventh. There is a drop thereafter which is probably due to fewer candidates remaining alive. The age figures for Negroes parallel the trends in the general population in regard to this disease.

The average age at the time of occurrence of the attack was 58.2 years; 57.2 years for males and 59.2 years for females. The very narrow difference bears out that the gap in age and incidence between sexes is closing rapidly.

LOCATION OF INFARCTION

We have classified the location of the infarcted area in our series. We categorized these locations as anterior, anterolateral, posterior,

TABLE VI

Location of Infarction in Negroes (1950–54)

	Males	Females	Total	Mortality rate (%)
Site				
Anterior	34	20	54 (41.5%)	42.6
Anterolateral	11	10	21 (16.1%)	52.4
Posterior	24	23	47 (36.1%)	42.5
Posterolateral	3	6	9 (6.3%)	77.8

and posterolateral. Table VI summarizes the results. The anterior wall was involved in 57.6 per cent of the cases and the posterior wall in 42.4 per cent. In the former category 41.5 per cent were purely anterior and 16.1 per cent anterolateral; and in the latter category 36.1 per cent were purely posterior and 6.3 per cent posterolateral. Thus, the ratio of anterior to posterior infarcts is roughly 3:2. We are not aware of any similar studies in Negroes aside from the report of Yater *et al.*[13] who found this ratio to be approximately 1:1 in Negro army personnel from 18 to 39 years of age. Table VI also suggests that the males suffered more anterior than posterior infarcts. The location of the infarct in this series did not seem to have any very definite bearing on mortality, except that extension of an anterior or posterior infarct to the lateral wall appeared to be associated with increased mortality.

SEASONAL OCCURRENCE

Attempts have often been made to study the effect of season on the incidence of acute myocardial infarction. Wolf and White[35] found that in New England, at least in 1926, most cases occurred from October to April. Bean and Mills[41] felt that coronary occlusion was most frequent in the winter, especially in north temperate climates. Master, Dack, and Jaffe[42] found a higher incidence in December and January, but in spite of this they did not think the season very important. Hoxie,[43] reporting from Los Angeles, stated that coronary occlusion there was definitely more frequent in the winter and early spring than in the late summer and early fall months. He considered the most potent factor probably the greater frequency of infection during the winter months. The studies of Yater *et al.*[13] would tend to show a slight drop during the summer and a slight increase in the fall and winter. Teng and Hayer[44] believe there is a significant increase in the number of cases of cardiac infarction coincident with the sudden onset of cold weather, and a slight increase with sudden warm or prolonged hot weather.

TABLE VII

Seasonal Incidence of Myocardial Infarction in the Negro (1950–54)

	Males	Females	Total
Spring	20	18	38 (29.0%)
Summer	18	10	28 (21.3%)
Fall	14	13	27 (20.7%)
Winter	20	18	38 (29.0%)

Our own experience (Table VII) indicates that the incidence of acute myocardial infarction is almost 10 per cent higher during the winter and spring than during the summer and fall. There was no significant trend as concerns the seasonal incidence in males and females and in fatal or surviving cases. We have no strong feeling on this point, but it seems reasonable to anticipate a rise in incidence during the winter with its hosts of related problems.

LIFE DURATION IN FATAL CASES

The question of the critical time period following the occurrence of an acute myocardial infarct is of more than academic importance. The various fatally terminating complications and the treacherous speed with which they may develop are too well known for enumeration here. However, the strict six-week bed rest period of former years has gradually yielded to the three-week period, and both may eventually yield to the armchair treatment. In spite of this the first two or three weeks are soberly respected by the most sanguine of physicians.

We have analyzed our fatal cases in terms of duration of life for four two-week intervals

TABLE VIII
Duration of Life in 61 Fatal Cases

Duration (weeks)	Number (%)
0–2	30 (49)
2–4	15 (25)
4–6	5 (9)
Over 6	11 (18)

following the occurrence of the infarct. As seen in Table VIII, 49 per cent of the patients died during the first two weeks, 74 per cent during the first four weeks, and 82 per cent during the first six weeks. The patients who died after six weeks succumbed chiefly to cardiac failure and cerebral embolization. In this analysis we have made no attempt to separate the "good risk" from the "poor risk" patients.

The data clearly indicate that the first two weeks, accounting for 49 per cent of the deaths, are the most critical. A significant number of fatalities occur during the next two weeks, so that in Negroes, as in whites, the first three or four weeks carry a very guarded prognosis.

Summary

The literature as it pertains to coronary artery disease in the Negro is reviewed. The distinctions formerly made in the literature as to basic racial differences between whites and Negroes relative to coronary artery disease and myocardial infarction are analyzed and refuted. Cognizance is taken of the trend from the attitude that the Negro does not feel coronary pain to one that he is insufficiently articulate to describe it. Also noted is the metamorphosis of thought from the idea that myocardial infarction is uncommon in the Negro to one that it is missed because dyspnea is substituted for precordial pain as the cardinal symptom. That part of the monumental work of Yater *et al.* which relates to myocardial infarction in Negroes is summarized.

Statistics are given from the Harlem Hospital, New York City, as representative of the Negro in a large northern urban community. Of a total of 312 cases of myocardial infarction admitted between 1950 and 1954, inclusive, 160 were excluded to produce a thoroughly proven series. Of the remaining 152 cases 21 were not those of Negroes. The remaining 131 Negro cases were then analyzed from the standpoints of incidence of predisposing factors, presence or absence of precordial pain, age, location of infarct, occurrence by season, and life duration in fatal cases.

The literature is reviewed as regards the association of hypertension with coronary artery disease. Diabetes mellitus is briefly treated as a grave predisposing factor to myocardial infarction with excerpts from the literature. In the series of cases presented it is shown that 71.1 per cent had predisposing factors. In this group the ratio of fatal to nonfatal cases was 1:1, whereas in cases without predisposition it was 2.5:1. Analysis of the fatal group showed that the ratio of cases with predisposition to those without predisposition was 4.5:1. Therefore, the Negro does not differ from the general population as regards the incidence of myocardial infarction in the presence of predisposing factors, nor are the mortality figures different in this race. Unless predisposing factors exist, the female has a better chance of survival than does the male.

Painless myocardial infarction and dyspnea as an interrelated symptom are discussed and the literature reviewed. It is shown that Negroes do not differ from whites in experiencing precordial pain. A total of 87.7 per cent of the patients in this series had precordial pain as a cardinal symptom. Precordial pain has no apparent influence on mortality, the incidence being 88.5 per cent in fatal cases and 87.1 per cent in nonfatal cases.

A sharp rise of incidence of infarction is noted in the fifth and sixth decades and continues at a high level in the seventh, with a decline thereafter. Here too the Negro does not differ from the general population. The average age of occurrence is 58.2 years. This also is statistically consonant with usual figures.

Study of the location of the infarcted area showed that 57.6 per cent had anterior and anterolateral infarcts, and 42.4 per cent had posterior and posterolateral infarcts, a ratio of about 3:2. No particular location appears to be most lethal.

The literature concerning seasonal variation

of incidence is briefly reviewed. In this series the incidence was almost 10 per cent higher for winter and spring than for summer and fall. Mortality figures show no seasonal trends.

Of the fatal cases 49 per cent died during the first two weeks, 74 per cent during the first four weeks, and 82 per cent during the first six weeks. Here again no racial differences are noted.

Conclusions

The previously abundant allegations in the literature that anginal pain is absent or rare in Negroes and that coronary artery disease and myocardial infarction are basically different, on racial grounds, in the Negro and white races, have not stood the test of more critical study. Analysis of a thoroughly typical series of 131 Negro cases of acute myocardial infarction admitted to the Harlem Hospital, New York City, between 1950 and 1954 inclusive, shows that the Negro does not differ from the general population when all factors are equalized in regard to (1) incidence in general, (2) sex incidence, (3) death rate, (4) predisposing disease, (5) symptoms, especially precordial pain, (6) age range, (7) seasonal incidence, or (8) life duration in fatal attacks.

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Experimental Studies

Electron Microscopy of Cardiac Nerves*

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IT IS common knowledge that the heart is richly supplied with different nerves from three sources, viz., from the sympathetic and the parasympathetic system of autonomic nerves and also by afferent nerves. There is general agreement about the nerve supply of the sinus region of the auricles and of the conductive system, but the nerve supply of the ventricles and its extent is still a much discussed question. From past physiologic experiences the nerve endings can be expected to exist in the following regions and these are the anatomic areas which we tried to study by means of the electron microscope:

(1) The endothelium and subendothelium;
(2) The muscle fibers;
(3) The capillaries and other blood vessels;
(4) The sites of stimulus production (sinus node) and stimulus conductivity (bundle of His, branches of Tawara and Purkinje fibers);
(5) The epicardium and the pericardium.

The following brief report will summarize our current investigations of the structure of the cardiac nerves and their locations. The investigations were performed on healthy guinea pigs and rabbits with fairly identical results.

THE SUBENDOTHELIAL NERVES

It has been proved in 1956[1] and 1957[2,3] that in the auricles as well as in the ventricles of mammals there is always present a homogeneous noncellular layer between the endothelial cells and muscle fibers which was named the subendothelial stratum. (Fig. 1.) In this layer the presence of vacuole-like bodies containing small osmiophylic enclosures is frequently observed. It was also emphasized[2,3] that these objects represent cross-sections of nerves, and this would indicate that the subendothelium is richly supplied by nerves comprising the afferent pathway of many reflexes which can be elicited from the endocardium (Francois-Franck, Bezold, Jarisch). This observation also challenges the still open question whether the endocardium should not also be able to produce painful or other sensations via these nerve axons. Just recently (1958) the

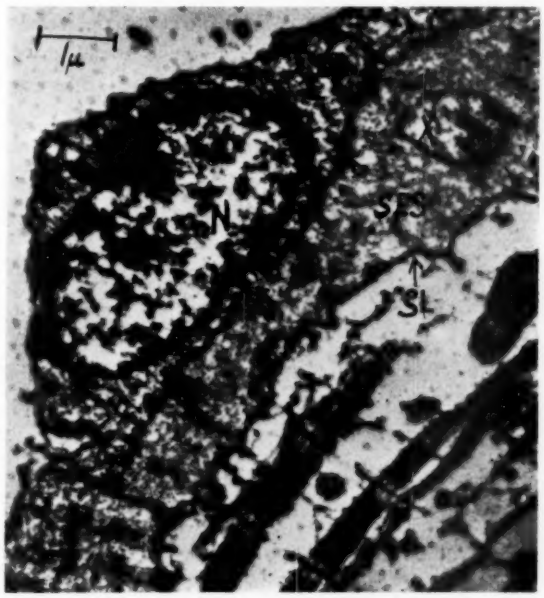

Fig. 1. Guinea pig auricle. E: endothelial cell. The arrows point to the basement membrane of this cell. SL: sarcolemma of a muscle fiber nearest to the endothelium. Between the basement membrane and the sarcolemma is a noncellular homogeneous subendothelial stratum (SES). X: cross-section of a nerve axon. Magnification 11,000×.

* From the Electron Microscopic Research Institute of the American College of Cardiology and Elmhurst General Hospital, New York, New York.

existence of this subendothelial stratum and also its content in nerve axons has been confirmed for the auricle of the turtle.[4]

The appearance of these subendothelial axons has been found up to now to be fairly uniform, the diameter being *ca.* 1–1$^1/_2$ μ. Most of them contain smaller bodies. Whether these represent plasmasomes or mitochondria or specific organelles of the nerve axons cannot yet be decided. Most of the axons are naked, some seem to be enwrapped in membranes besides the individual membrane of each axon.

The Interfibrous Nerves

As just mentioned, the subendothelial stratum contains many nerves but they do not penetrate between the individual endothelial cells. In a similar way nerves and nerve endings have not been found inside the muscle fibers of the heart, between the sarcosomes and miofibrils; but they can be found between the different muscle fibers in the auricle as well as in the ventricle. Not infrequently they appear there as bundles of axons, surrounded by the sheath of a Schwann-cell whose nucleus is often well recognizable. Most striking is the difference in the size of the axons in such a bundle. As Figure 2 shows, the diameter can vary in the same nerve fiber between 3 to 4 μ and one-half to one-third of a micron. The cross-sections of these axons are partly homogeneous; they also contain dark osmiophylic bodies and partly small vacuoles. Each of these axons has an outer membrane and they are all embedded within the nerve fibril in a homogeneous matrix which contains very small droplets.

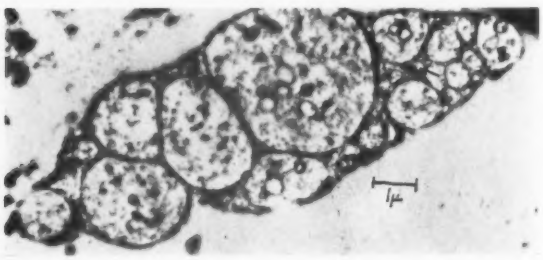

Fig. 2. Nerve fibril from the left ventricle of the rabbit. Surrounded by a membrane it contains in a matrix with very small droplets (arrow) cross-sections of axons of very different sizes. The biggest has a diameter of about 4 μ, the smallest a diameter of about $^1/_3$ μ. Magnification 6,000×.

The Nerve Supply of Capillaries in the Heart

An astonishing finding was the very rich supply of capillaries with nerves in the auricle as well as in the ventricles. Of course it has been known for a very long time that the capillaries of the body are under the influence of sympathetic nerves, which produce by their activity a contraction, occasionally also dilatation, of the capillaries. However, the capillaries of different organs seem to vary in their abundance of nerve supply. I have not yet found them on the capillaries of the lung but they are in great abundance on those of the heart.

Sometimes such a single nerve axon is in direct contact with the capillary wall (Fig. 3);

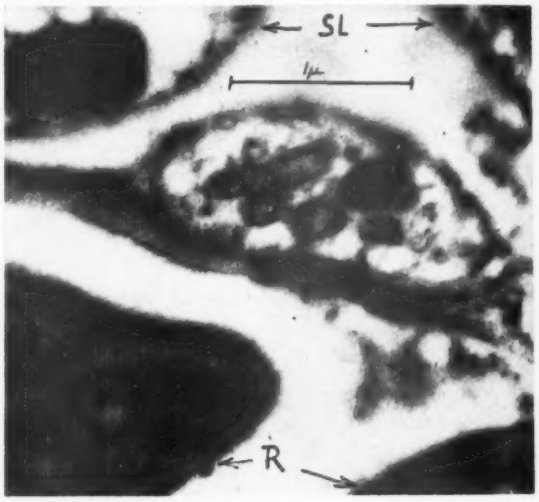

Fig. 3. Capillary of a guinea pig, right ventricle. Adjacent to the capillary is a nerve axon; inside the capillary are red blood cells (R). The capillary and the axon lie between two myofibrils. SL: Their sarcolemma. Magnification 25,000×.

sometimes it is in contact with the surrounding Rouget cells (perycytes) and sometimes one or two or an entire group of them lie only in the neighborhood of the surrounding Rouget cells (Fig. 4). The cross-section of the axons within a surrounding membrane may show a few cylindric osmiophylic bodies (either plasmosomes or not yet known organelles) but very often

Fig. 4. Guinea pig left ventricle near aorta. Capillary between two muscle fibers. SL = sarcolemma; SS = sarcosomes; N = nucleus of the endothelial cell of the capillary; P = perycyte. Near the perycyte are a bunch of axons (A), cross-sectioned or diagonally sectioned. The inner finest fibrils with a diameter of 200–400 A° can be seen as small dots and lines. Magnification 12,000×.

in addition to these bodies, the axons near the capillaries contain extremely fine fibrils which can be seen in cross-sections as little dots and in diagonal sections as fine lines. Some cross-sections of these axons show these very fine dots and lines exclusively and no larger darker bodies.

It seems probable that this rich nerve supply of the capillaries of the heart is responsible for the intense pain in conditions of sudden inadequate blood supply as in attacks of coronary spasm.[7]

We are not able as yet to attribute certain appearances of all these unmyelinated nerves to a certain type of nerves (sympathicus or vagus). However, the existence of a uniform appearance of the subendothelial axons hints that these are the afferent axons, because nothing is known about the supply of the endothelium with efferent nerves. However, the variable appearance of nerves supplying the capillaries may indeed represent different types of nerves for these vessels.

The same conclusion applies to the different axons contained in the interfibrous nerve fibrils of the auricles and the ventricles. Here we know from physiologic experiences of the influence of sympathetic and parasympathetic nerves and the probable existence of afferent nerves. It seems without any doubt that in such nerve fibers the very thick axons are of a different type than the very thin ones, in spite of the fact that in longitudinal sections the width of such an axon changes continuously. Studies of the very thin axons of the myelinated type have been made repeatedly[5,6] and they have also been observed in the non-myelinated cardiac nerves (Fig. 2) and recently also in the turtle's auricle.[4]

It is only a small part of the great chapter,

"the cardiac nerves," that has been covered up to now by our research. A more detailed report will follow in the near future as our studies continue.

Summary

With methods of electron microscopy the location and the appearance of nerve axons supplying the auricle and ventricle of the mammalian heart have been investigated.

The nerves in the subendothelial stratum, those reaching the capillaries, and the thick as well as the ultra thin axons between the muscle fibers in auricles and ventricles are described and representative pictures are presented.

It is suggested that the pain in angina pectoris is mainly due to the rich supply of the capillaries of the heart with centrifugal nerves.

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Review

The Pharmacologic Approach to Coronary Insufficiency*

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THE HEART, in common with all other muscle, depends upon its blood supply for nourishment. This is supplied by the coronary arteries. When this is diminished the mechanical efficiency of the myocardium as a pump is impaired. When the coronary artery blood supply to the heart is completely occluded the muscle will die. The systolic pressure for the flow of blood through the coronary circulation is essentially the same as the aortic pressure since the coronary artery has its origin in the aorta.

An adequate blood supply to nourish the heart can be maintained only if (1) the aortic pressure is sufficient; (2) the blood flowing through the coronary circulation provides the necessary nourishment; (3) the lumen of the coronary vessels is not narrowed by spasm or plaques; and (4) they are not occluded by the presence of infarcts. With moderate decreases in aortic pressure the coronary circulation remains adequate; however, reductions in aortic pressure may embarrass the coronary circulation even if the vessels are normal. It is clear that a marked reduction in red cells in blood of the coronary circulation may so diminish the oxygen supply that myocardial hypoxia may prevail. However, the most prevalent causes of coronary insufficiency lie in the vessels, namely, narrowing of the lumen by spasm or by plaques on their intima.

Since 1867 when the distinguished English therapist, Lauder Brunton, used amyl nitrite to relieve the pain of angina pectoris, the pharmacologic approach to coronary insufficiency has been directed toward coronary dilatation with its concomitant increase in myocardial blood supply. The mechanism of action of the various drugs used to achieve coronary dilatation and their advantages and disadvantages are discussed in this review.

PHARMACOLOGIC EXPERIMENTAL PROCEDURES

The pharmacologist is constantly on the alert for drugs which will exert a specific dilating action on the coronary vessels. Therefore, through the years he has developed methods experimentally to test the action of drugs on these structures.

Morawitz and Zahn[1] developed one of the first generally used procedures. The test animal is the anesthetized dog in which a suitable anticoagulant such as heparin has been injected. The thoracic cavity is opened and a special cannula is inserted into the coronary sinus through an incision in the right auricle. The cannula is sutured into the right auricle and made tight in the coronary sinus by means of a rubber dam inflatable from the outside. The blood flows out of the cannula. It is measured and its rate determined. The blood is immediately returned to the general circulation into the jugular vein. Many refinements of the procedure have been employed to measure the coronary flow of blood. The method serves as a useful laboratory procedure to determine coronary flow *in situ* as a more or less routine experiment. The coronary sinus blood has been

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shown to represent a variable portion of the coronary venous outflow. This is especially true under conditions of altered contraction of the myocardium as produced by many drugs which stimulate the muscle. Therefore, this method does not give an absolute measurement of the coronary flow.

Barbour and Prince[2] studied coronary flow in the perfused isolated rabbit's heart. The perfusion is made through the aorta, and the defibrinated blood of the sacrificed animal diluted with Locke-Ringer's solution is the perfusate. The drugs to be tested are dissolved in the perfusion fluid after a satisfactory norm is obtained. The time required for the perfusion of a definite volume of solution is taken as a measure of coronary flow. The method gives excellent results with many of the more potent coronary dilators such as the nitrites.[3] This perfusion method was developed by Langendorff[4] in 1895, using the isolated cat's heart. Many investigators have modified and improved the procedure so that today modifications of the Langendorff heart preparation have become a recognized procedure for screening coronary dilator drugs.

Voegtlin and Macht[43] used successfully a smooth muscle preparation consisting of rings joined in tandem from the circumflex and descending coronary vessels from the heart of a steer. By means of this isolated coronary preparation, these and other investigators have tested many drugs on the coronary arteries. Voegtlin and Macht were the first to show that morphine relaxes the coronary vessels. This has been confirmed by Elek and Katz.[5] Wégria and associates[6] observed that 2.5 to 5 mg/kg of morphine sulfate given intravenously to dogs did not significantly affect the coronary flow. In some animals there appeared evidence of an increase in coronary resistance. Frequently, contradicting data such as these are recorded with regard to the effect of drugs on coronary flow. They arise from species variations and totally different procedures of measurement.

Essex *et al.*[7] used the thermostromuhr to measure coronary flow in the dog. The device was sutured around the circumflex branch of the left coronary artery and the wires brought to the outside. The animal was allowed to recover completely from the operation, and then drugs were tested on coronary flow in the intact, unanesthetized animal. The principle of the thermostromuhr depends upon temperature differences produced by increased or diminished blood supply in the vessel (dilatation or constriction) on which the device is attached. These are recorded by means of a thermocouple. Critical evaluation of the method has shown it to be subject to many artefacts. These are caused by changes in blood temperature, the occurrence of back flow in the vessel, and the movements of extravascular fluids in the immediate vicinity of the recording instrument.

Eckenhoff and Hafkenschiel[8] measured the coronary action of various drugs on the spontaneously breathing heparinized dog. They used a bubble flowmeter to measure the coronary flow. They contend that the proper evaluation of a drug on coronary flow must correlate the ratio between the oxygen supplied to the myocardium and the oxygen demand of the myocardium. This they refer to as the "nutritional index." Also, consideration must be given to the efficiency of muscle cells in making the energy transformations necessary to perform the work of the heart. Their approach appears to go beyond most of the procedures employed by previous investigators and represents a distinct advance in the evaluation of coronary dilators. Of a number of coronary dilators studied by these criteria they found papaverine to be most efficient.

Goodale *et al.*[9] applied the nitrous oxide method of measuring blood flow to the measurement of coronary artery flow. The arteriovenous nitrous oxide differences are measured from femoral arterial blood and coronary sinus venous blood. The latter is obtained by catheterization of the coronary sinus. This method has been applied to the study of coronary flow in man by Bing.[44] The results were found to correlate well with those obtained by other methods.

Although no one method has been wholly satisfactory, much progress has been made in overcoming the inaccuracies and unphysiologic conditions imposed by earlier methods. The normal rate of flow to the heart appears to be about 60 to 70 cc/100 g myocardium/min.

Coronary vasodilatation resulting from anoxia and other causes is capable of causing a threefold or larger increase in the supply. A drug which would simulate the action of these metabolic products in effecting a relaxation of the smooth muscle of the coronary arterioles might serve as a pharmacologic agent for conditions of coronary insufficiency.

With these and many other experimental procedures available it is obvious that the question of whether or not a drug is a coronary dilator can be answered. In addition, the quantitative aspects of the procedures compare quite favorably with other biologic methods. The difficulty appears in correlating these laboratory measurements with the efficacy of the drug in coronary disease. It has been mentioned that papaverine was shown to be the most efficient among a number of coronary dilators. Yet clinically the drug has been most disappointing. Our knowledge of a drug to be useful in coronary insufficiency must embrace the following components, as suggested by Wégria:[6] (1) the effect of the drug on coronary flow; (2) the mechanism of its action; (3) the effect of the agent on the ratio cardiac work/coronary flow; and (4) the influence of the compound on the efficiency of the heart in its work performance.

Coronary Dilator Drugs

GLYCERYL TRINITRATE

Therapy for the relief of acute pain in angina pectoris or coronary occlusion is predicated upon the use of promptly acting coronary dilators to relieve the cardiac ischemia. For this purpose glyceryl trinitrate is the most effective and dependable drug. The drug acts directly on the musculature of the vessels irrespective of their autonomic innervation. The sublingual administration affords rapid action and bypassing the portal circulation. Many clinicians prefer the hypodermic tablets instead of the tablet triturates on the basis of more rapid absorption.

The exact mechanism of the vasodilatation evoked by glyceryl trinitrate is not clearly understood. Krantz, Carr, Forman, and Cone[10] showed that the organic nitrates, including glyceryl trinitrate, elicit their vasodilation by virtue of their own molecular structures and not through hydrolysis and subsequent reduction to nitrite. Heppel and Hilmore[11] isolated an enzyme from hog's liver which catalyzed the reduction of glyceryl trinitrate to nitrite by glutathione. Glutathione appeared to react with glyceryl trinitrate *in vitro* to form the trinitrite before hydrolysis occurred. This reaction, however, is a slow, orderly, time process, whereas the response to glyceryl trinitrate is almost immediate and evanescent. As glyceryl trinitrite is very unstable and is decomposed immediately by water and air (Masson, 1883), we feel that this is further evidence of the vasodilating action of glyceryl trinitrate as such and not after reduction to organic or inorganic nitrite.

Krantz, Carr, and Bryant[12] demonstrated that glyceryl trinitrate inhibited adenosine triphosphatase (ATPase) in the rabbit's aorta. The inhibition of the enzyme ATPase will reduce the rapidity of breakdown of the energy-rich phosphate system adenosine triphosphate (ATP). If through the decomposition of ATP by its enzyme ATPase, tone and constriction of the artery are maintained, it is possible that a drug which acutely relaxes the artery may do so by interfering with the activity of ATPase. This would terminate the decomposition of ATP and consequently terminate the source of abundant energy required for tonus and constriction; hence the vessel would respond by relaxing. Indeed, additional work at an enzyme level is necessary in order to delineate more clearly the mechanism of coronary dilatation afforded by glyceryl trinitrate.

The use of vasodilator drugs routinely in coronary occlusion is predicated upon their effectiveness in increasing coronary flow and aiding in establishing collateral circulation. This should not be done at the expense of imposing an additional work load on the heart. This latter effect is less marked with glyceryl trinitrate and related compounds than with other coronary dilators. In addition, Zoll and Norman[13] found glyceryl trinitrate to be the only one of the commonly-used vasodilators capable of encouraging collateral circulation and the only substance able to prevent experimental myocardial infarction by coronary oc-

clusion. This adds additional evidence to the validity of the use of this drug for more than three-quarters of a century.

OCTYL NITRITE (OCTRITE)

In a study of the pharmacology of alkyl nitrites, Krantz, Carr, and Forman[3] developed the use of octyl nitrite. The formula of amyl nitrite is $C_2H_{11}ONO$, that of octyl nitrite is:

$$CH_3.CH_2.CH_2.CH_2.\underset{\displaystyle C_2H_5.}{\underset{|}{CH}}.CH_2.ONO.$$

It is 2-ethyl-*n*-hexyl-1-nitrite. This substance does not possess the disagreeable odor that is characteristic of amyl nitrite. Besides, its vapor pressure is only 3.3 mm at 25° C. This permits the substance to be used in an inhaler. The action of octrite on the coronary flow is just as prompt as that of amyl nitrite. It offers great advantages in the technic of medication. The authors found that octrite gave rise to less methemoglobin than did amyl nitrite and that its response was slightly longer than that of the more volatile ester.

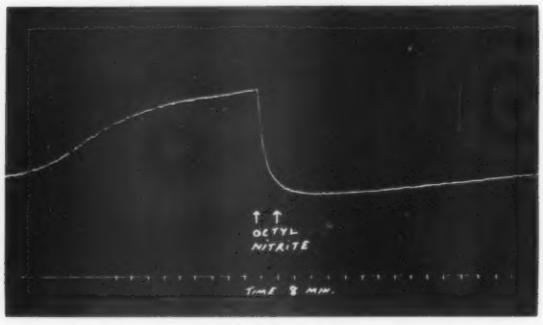


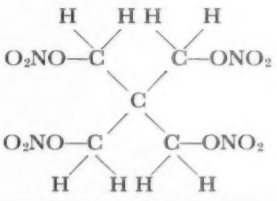
Fig. 1. The action of an organic nitrite (octyl nitrite) on the isolated coronary vessels of the steer. (From Krantz, Carr, and Forman: *J. Pharmacol. & Exper. Therap.* 64: 302, 1938, permission Williams & Wilkins, Baltimore.)

Freedberg, Spiegl, and Riseman[14] studied octrite extensively and compared it with glyceryl trinitrate in its capacity to enable anginal patients to do work without developing anginal pain. Russek and Anderson[15] studied the relative efficacy of octyl nitrite and glyceryl trinitrate in coronary insufficiency. They observed that the inhalation of octyl nitrite from the inhaler elicited a therapeutic response comparable to the sublingual administration of $^1/_{300}$ to $^1/_{200}$ gr glyceryl trinitrate.

Newer types of inhalers are now available for medication with octyl nitrite (medihaler-nitro). These provide rapid response and dependable dosage. This is made possible by formulation of octyl nitrite with a nontoxic propellent under pressure in a container with a single dose valve. The degree of nebulization and volatilization of the propellent are conditioned by the nozzle and the chamber. As octyl nitrite is a stable compound this form of administration appears to offer advantages.

PENTAERYTHRITOL TETRANITRATE (PERITRATE®)

This substance is a newer vasodilator of the nitrate series. Its structure is shown in the accompanying formula:



Peritrate (pentaerythritol tetranitrate)

The compound is a white crystalline powder.

Pentaerythritol tetranitrate elicits a pharmacologic response similar to glyceryl trinitrate. Its action as a vasodilator is far less marked than that of glyceryl trinitrate. It is used routinely as a prophylactic coronary dilator in angina pectoris. It reduces the amount of glyceryl trinitrate required by anginal patients. Reports in the literature of the use of pentaerythritol tetranitrate indicate that the drug has a definite place in the treatment of coronary insufficiency.

Winsor and Humphreys[45] used peritrate in 125 anginal patients and observed satisfactory improvement in 75 per cent of the cases. Weitzman[16] found the drug useful in cases of coronary insufficiency, but in many cases it did not suffice as a substitute for glyceryl trinitrate. Russek *et al.*[17] evaluated several coronary dilators in patients using the Master 2-step exercise test. They found Peritrate to be the most effective agent in preventing electrocardiographic changes and the pain syndrome. They prefer Peritrate for prophylactic treatment.

Tolerance to Peritrate does not readily develop. The side effects are headache, lethargy, gastrointestinal disturbance, and occasional visual disturbance. Seldom are these side effects sufficiently severe to necessitate the withdrawal of the drug.

The usual dose range of Peritrate is 10 to 20 mg (1 or 2 tablets) three to four times daily.

TRIETHANOLAMINE TRINITRATE (METAMINE, NITRETAMIN®)

This organic nitrate is available as its diphosphate salt, as shown in the formula:

$$N(C_2H_4ONO_2)_3.2H_3PO_4$$

Triethanolamine Trinitrate Diphosphate

Triethanolamine trinitrate diphosphate occurs as a white crystalline powder which is sparingly soluble in water.

Triethanolamine trinitrate is a potent dilator of the coronary vessels. Its action is similar to that of glyceryl trinitrate but more sustained. Melville and Lu[18] observed that the molecule of triethanolamine trinitrate is more refractory to hydrolysis than is glyceryl trinitrate. This is likely a factor in providing a more sustained action.

Triethanolamine trinitrate has been used by numerous investigators to assess its value in the treatment of coronary insufficiency. In general, the clinical response to the drug is good. For example, Fuller and Kassel[19] found the compound valuable in 82 per cent of a series of 71 patients in preventing anginal attacks. They believe it to be the most effective coronary dilator. There is no general agreement among clinicians with regard to the most effective coronary dilators.

Tolerance to triethanolamine trinitrate appears to be rare. Untoward effects encountered are headache, gastric pain, vomiting, dizziness, and palpitation. Like other organic nitrates the compound is contraindicated in glaucoma.

Triethanolamine trinitrate in the form of its diphosphate salt is available in 2 mg tablets. The usual daily dose is 4 to 5 tablets spaced throughout the day. In the acute attack glyceryl trinitrate should be used.

THEOPHYLLINE PREPARATIONS

Theophylline is a white crystalline powder. It is stable in the air and evokes a bitter taste. The compound is sparingly soluble in water (1 to 120) but freely soluble in solutions of alkalies with which it combines to form salts. Theophylline is more frequently employed in the form of soluble derivatives or mixtures. The most popular of these is aminophylline, which is theophylline and ethylenediamine. The ethylenediamine renders the compound soluble and effects a more dependable absorption from the gastrointestinal tract. The other U.S.P. theophylline preparation is theophylline and sodium acetate.

One of the disadvantages of the various theophylline preparations is the gastrointestinal distress which they cause in a large number of individuals. This becomes particularly manifest when the dosage levels are increased. Indeed, this is unfortunate because it hampers intensive therapy with the drug and a more complete exploration of its possible benefits.

Theophylline can be shown to be a definite dilator of the coronary vessels in laboratory animals. Eckenhoff and Hafkenschiel place aminophylline second on their list of coronary dilators when viewed from its capacity to increase the nutritional aspects of the myocardium and aid in the energy conversion necessary for the heart cells to perform their maximal work. It would appear, therefore, that theophylline preparations would be routinely useful in coronary insufficiency. Unfortunately, however, there is no unanimity of clinical opinion with regard to the value of the theophylline derivatives.

Gold *et al.*[20] studied xanthine compounds in the treatment of 100 patients with coronary disease. They used the xanthines and placebos. Their findings were not confirmatory of the value of xanthine compounds including theophylline. On the other hand, Levy *et al.*[21] found that aminophylline delayed the occurrence of pain in persons with coronary disease. Furthermore, Le Roy[22] used placebos and aminophylline in 68 cases of coronary disease over a period of two years. His observation was that aminophylline effected benefit in 75 per cent of the cases, whereas a sedative and a placebo are helpful to only 20 per cent of the individuals.

It is our opinion that the limitation of the

dosage, owing to gastrointestinal symptoms, and the assumption that absorption is complete are likely responsible for variations in results observed by various investigators. Truitt *et al.*[23] developed a comparatively simple method for theophylline blood levels. In exploratory tests they found that the blood levels of the theophylline varied greatly in different individuals on the same dosage schedule. The availability of such a test may prove very helpful in placing the therapy with theophylline on a more scientific and satisfactory basis.

Other methods for the estimation of blood levels of theophylline have been developed by Waxler and Schack.[24] These authors and Truitt *et al.*[23] studied blood levels of theophylline in patients when administered under various conditions. The latter found that approximately 0.5 mg % is necessary for diuresis with the compound. They observed excellent absorption from the administration of plain tablets (not enteric coated). A retention enema yielded blood levels comparable to those obtained by intravenous injections. Absorption from rectal suppositories was capricious and uniformly poor. Waxler and Schack demonstrated that theophylline did not enter the human red blood cell, and from animal experiments their data indicate that theophylline remains in the extracellular compartment of the body.

It occurred to Krantz *et al.*[25] to unite theophylline with the simple amino acid glycine and prepare theophylline with sodium glycinate (Theoglycinate). The mixture is less alkaline than the usual theophylline preparations and appears to be well tolerated in the gastrointestinal tract. Paul and Montgomery[26] used Theoglycinate® in the treatment of patients with coronary disease and were able to give up to 2 g of theophylline in a day without gastric distress. Bubert and Cook[46] using Theoglycinate in the treatment of asthma, reported similar tolerance with the mixture. With a clinical test for theophylline blood levels, it is possible that in the near future our data on the value of the drug in coronary disease will be less controversial.

In the interim, however, it is our opinion that the drug is warranted routinely in angina and postcoronary conditions. The pharmacologic basis for its use is sound. The drug is comparatively nontoxic, and side effects of an untoward nature are not so severe. Besides, there is as yet no adequate substitute for theophylline.

Aminophylline is generally prescribed in 0.2 g tablets three or four times a day. Aminophylline contains about 75 per cent of theophylline. The compound is also available intravenously and intramuscularly.

Other solubilized theophylline dosage forms are: theophylline sodium acetate, N. F., theophylline isopropanolamine (Theopropanol®), theophylline methyglucamine, N. N. D. (Glucophylline®), theophylline monoethanolamine (Monotheamin®), theophylline dihydroxypropyl, N. N. D. (Hyphylline), and theophylline cholinate (Choledyl®).

Pharmacologic Approach to Cholesterol Metabolism

Many individuals with coronary occlusion have an elevated serum lipid level. The serum phosphorus level, however, is not proportional to the elevated cholesterol level, i.e., there is an increase in the cholesterol-phospholipid molar ratio. This ratio is apparently the important factor. The diminished level of the phospholipid emulsifiers does not adequately maintain the colloidal suspension of cholesterol. Cholesterol and fat deposits in the arterial lumen contribute to the coronary atherosclerosis. In addition, Gofman *et al.*[27] showed the presence of large, low density lipoprotein molecules in the sera of patients with coronary occlusion. This also may be a component in the etiology of the disease.

However, in addition to the significance of cholesterol in the pathogenesis of coronary artery lesions, the anatomic and physiologic condition of the arterial tissue undoubtedly plays an important role. Thannhauser[28] states, "The mechanism of cholesterol accumulation in the arterial tissue cannot be explained by the one-sided investigation of the physical properties of the lipid constituents and their protein aggregates (lipoproteins) in the plasma. The anatomic and physical properties of the arterial tissue are of equal importance in the accumulation of cholesterol in this tissue."

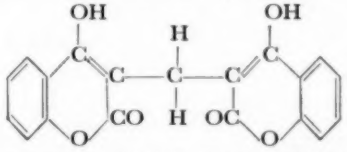
Nicotinic Acid: The pharmacologic approach to this problem at present cannot envisage the modification of anatomic defects in the coronary vessels *per se*. Altered physiologic states such as spasticity can be modified by the use of the vasodilating drugs. The problem of prevention of future atheromatous plaques with drug therapy has been attacked within recent years. Parsons *et al.*[29] demonstrated that massive daily doses of nicotinic acid diminished hypercholesterolemia. Parsons and Flinn[30] administered 3 to 6 g of nicotinic acid daily to 24 patients with hypercholesterolemia. Significant drops in blood cholesterol levels were obtained in 16 of this group of patients. The flushing produced by these comparatively high doses of nicotinic acid subsided the first week of therapy. Discontinuance of nicotinic acid resulted in increase of blood cholesterol levels. Nicotinamide could not be substituted for nicotinic acid in these experiments. This is a most interesting observation and bids fair to have very useful applications. The mechanism of the action of nicotinic acid in hypercholesterolemia remains obscure. Since, however, in these cases the treatment was carried out while the patients were on their customary diets, it would appear that nicotinic acid either inhibits cholesterol synthesis or promotes its catabolism.

Sitosterol: The nature of the fat ingested appears to be an important factor in determining whether or not it will contribute to the formation of atheromatous plaques. Animal fats and hydrogenated (saturated) vegetable oils raise the serum cholesterol while unsaturated fish oils tend to lower the serum cholesterol level. Although cholesterol has been shown to be closely associated with atherosclerosis, it is generally agreed that it is not the sole factor in the etiology of the disease. However, control of the cholesterol level of the blood appears feasible, and agents that will accomplish this provide an experimental type of therapy in atherosclerosis.

For this purpose a plant sterol, beta sitosterol, was introduced into therapy under the name of Cytellin. Cytellin is a mixture of 80 to 90 per cent beta sitosterol and 10 to 20 per cent dihydro-beta sitosterol. Beta sitosterol is a plant sterol chemically identical to cholesterol, except for an ethyl group on the side chain. Dihydro-beta sitosterol has a saturated ring. The sitosterols apparently enhance the fecal excretion of cholesterol. They accomplish this presumably by interfering with the absorption of cholesterol from the intestine. Thus, less exogenous cholesterol from food is absorbed, and endogenous cholesterol secreted in the bile is not reabsorbed. The serum cholesterol level is lowered as a result of the sustained decreased absorption of this substance. Doses of 10 g/day or larger have been used to provide a prolonged low blood cholesterol level. Cytellin has been used in the reduction of the hypercholesterolemia of diabetes mellitus, hypothyroid states, nephrosis, and xanthomatosis. There is little agreement as to its value in atherosclerotic disease. The sitosterols have not produced serious toxic effects in patients to whom they have been administered in large doses for as long as two years. Their ultimate possibility of toxicity is unknown.

Anticoagulant Therapy

Shofield[31] in Canada and Roderick[32] in the United States demonstrated that hemorrhagic diathesis in cattle occurred when they ingested improperly-cured common sweet clover hay, or silage. This condition was shown to be due to prothrombin insufficiency by Roderick and Schalk,[33] Quick,[34] and Link.[35] In 1941, Link and his associates showed that the substance responsible for the hemorrhagic diathesis, present in the spoiled sweet clover, was a coumarin derivative. The compound isolated and later synthesized was dicumarol, which has the structure shown in the accompanying formula.



Bishydroxycoumarin, U.S.P., dicumarol (dicoumarin) 3,3′-methylene-bis-(4-hydroxycoumarin)

The principal action of dicumarol is to prolong the clotting time of blood. It is readily absorbed from the gastrointestinal tract and is active when administered orally. The anticoagulating property of dicumarol depends upon its capacity to diminish the prothrombin level

of blood. After the administration of the compound there is a latent period of 24 to 48 hours. Then a gradual decrease in prothrombin takes place. The maximal decrease occurs in three to five days, and the action of the drug diminishes during the next three to five days.

The actual mechanism of the hypoprothrombinemia produced by dicumarol probably is due to a depression of prothrombin synthesis.[36] This is caused by an inability to utilize vitamin K. Witts[37] points out that there is a basic similarity between the chemical constitution of 2-methyl-1,4-naphthoquinone (vitamin K fraction) and 4-hydroxycoumarin. This suggests that dicumarol might exert its action by interfering with the utilization of vitamin K by the liver. Indeed, the action of dicumarol in producing hypoprothrombinemia can be explained by postulating that dicumarol displaces the prosthetic group of vitamin K.

The use of dicumarol and other anticoagulants in postcoronary patients is well established. Its value stems primarily from its capacity to produce hypoprothrombinemia and thus diminish the possibility of intravascular clotting in the coronary arteries producing infarction. Another possible component of its action was demonstrated by Gilbert and Nalefski.[38] They studied dicumarol on the coronary vessels of the dog. Dicumarol was shown to be a definite coronary dilator. Their results showed that this anticoagulant drug evoked increases in coronary flow comparable to theobromine. They expressed the view that the value of these drugs in angina pectoris and coronary thrombosis may be largely due to their effect on coronary dilating response.

Wise, Loker, and Brambel[39] reported their findings of thromboembolic complications following surgery with and without dicumarol therapy. Their observations include over 12,000 patients. Their data showed a significant reduction in the incidence of venous thrombosis when dicumarol was employed. Fibrinogen determinations revealed no evidence of toxicity from dicumarol. They emphasize the necessity for meticulous standardization of the laboratory procedure for gauging the dicumarol effect if the best results are to be achieved in the prophylaxis program.

Of special interest is the study of dicumarol in acute coronary thrombosis. Peters, Guyther, and Brambel[40] observed an increased clotting tendency in most of their coronary patients. They studied 110 cases of coronary thrombosis with myocardial infarction. Fifty patients were given dicumarol and 60 were not given the drug. Their observations extended over two and one-half years. In the patients receiving the anticoagulant the occurrence of embolic phenomena was reduced to one-eighth and the mortality rate to one-fifth of that in the untreated patients. These results have been extended and confirmed.

Schilling[41] studied 120 cases of myocardial infarction. Half received anticoagulants, and half did not. The incidence of thromboembolic complications was 25 per cent in the control group and 5 per cent in the treated group. Indeed, these benefits are significant both clinically and statistically.

These findings were substantially confirmed by Wright *et al.*[42] in a study of 1,031 cases of myocardial infarction with and without anticoagulant therapy. Thromboembolic phenomena occurred in 29 per cent of the control group and in only 9 per cent of the treated patients. They state, "There is a real risk to the patient in waiting for the course to worsen or the first thromboembolic complication to develop before using anticoagulants." The beneficial use of anticoagulant therapy in cases of coronary insufficiency with infarction appears to be established.

Summary

The use of pharmacologic agents in coronary insufficiency has been reviewed. The mechanism of action of various drugs has been discussed with special reference to those of the nitrite-nitrate series. A discussion of pharmacologic agents designed to reduce hypercholesterolemia is included. The place of anticoagulant therapy is delineated. It is clear, however, that basic knowledge in this disease is in its incipiency and further precise knowledge of the mechanism of our most effective drugs is fragmentary.

A need for more effective drugs is urgent. More work at an enzyme level is required to determine the biochemical lesion responsible for coronary spasticity and insufficiency with

occlusion. The hope for the future is figuratively expressed in the cogent statement of Sir Frederick Hopkins, "In a country rich in gold observant wayfarers may find nuggets on their path, but only systematic mining may provide the currency of nations."

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Report on Therapy

Circulatory Overloading During and Following Blood Transfusion*

A Method of Prevention Using Packed Red Cells and Injection of Morphine and Atropine

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It is difficult to estimate the frequency of circulatory overloading during and following transfusions because such occurrences are seldom reported. Personal experiences indicate that it occurs much more often than is generally realized. Riddell[1] described circulatory overloading as the commonest cause of death following transfusion, and Drummond[2] considers it only slightly less important than incompatibility.

As will be noted later, this complication following transfusion may selectively occur in patients with chronic congestive heart failure, chronic anemia, prolonged fever and acute or chronic pulmonary disease. If transfusions are definitely required in such patients, packed or sedimented red cells should be used, the transfusion should be given slowly and, in addition, we believe that it should be preceded by an injection of morphine and atropine. Another injection of morphine and atropine should be given about half way through the transfusion. This paper describes the rationale for these prophylactic injections.

It seems remarkable that only general cautions against circulatory overloading are mentioned in the various books on blood transfusions.[3] One of the best prophylactic measures is the use of concentrated or packed red cells.[4] By this method the volume is decreased by about half and the sodium content is greatly reduced. The point made by Ginsberg, Frank, and Gubner[5] that the patient sit upright during the transfusion seems vitiated by the finding by Sharpey-Schafer[6] that reclining reduces the right atrial pressure. On the other hand, Vugrincic's[7] recent suggestion that less left ventricular work is required to expel blood in the upright than in the recumbent position, would favor the sitting position. Another prophylactic method, besides the one herein described, is based on the finding by McMichael and Sharpey-Schafer[8] that digoxin lowers the right atrial pressure. Scott's[9] recommendation that 1.0 to 1.5 mg of digoxin be given by intravenous injection immediately before transfusion would therefore be a rational procedure. Undoubtedly, Scott means that the amount would only be given before the first transfusion.

In this study, we did not consider the administration of hypotonic, hypertonic, or isotonic solutions which would involve electrolyte and solution transfer exchanges creating additional volume alterations. Only blood transfusion reactions were considered.

Clinical Features and Treatment of Circulatory Overload

The clinical symptoms resulting from over-

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loading of the circulation usually begin with a dry cough and a constriction of the chest. Cyanosis and dyspnea soon appear and if overloading has been marked or continuous, blood-stained frothy sputum appears. Coincident with these symptoms, tachycardia develops, the cervical veins become distended, and coarse and fine rales are heard over the entire chest. The symptoms may appear during or shortly following the transfusion; sometimes the symptoms follow after a chill and fever.[9]

The treatment of circulatory overloading following transfusion must start at the earliest possible moment of detection. The cervical veins should be watched closely, and at the first signs of engorgement the transfusion should be stopped. A dry cough that develops during the transfusion should also be considered as evidence of circulatory overload, and the transfusion should be stopped immediately.

Morphine gr $^1/_4$ (15 mg) and atropine gr $^1/_{150}$ (0.4 mg) should be given at once. Scott[9] recommends gr $^1/_{50}$ (1.2 mg) of atropine. Oxygen should be given by a face mask or other acceptable method. Venous pressure must be reduced as soon as possible by phlebotomy or application of tourniquets on all four limbs and later followed by phlebotomy if improvement is not apparent. The fully developed pulmonary edema cannot always be treated successfully, so that the prophylactic method described assumes great importance.

The prophylaxis of this condition is obviously very important, since as stated above, this complication is most likely to occur in certain types of patients. In these patients, transfusions should be given only if urgently required. If it is ascertained that transfusion is definitely indicated in this type of patient, then several methods can be used to minimize or protect against the overload effects. Aside from the methods so far recommended, such as using packed washed red cells or sedimented red cells, the sitting-up posture during transfusion and the slow infusion of the blood (about 1 cc/kg/hr[10]), we have found another simple procedure to have a salutary effect in this type of patient.

A hypodermic containing morphine sulfate gr $^1/_4$ (15 mg) and atropine sulfate gr $^1/_{150}$ (0.4 mg) is prepared, and the patient is given one-half of the contents about five minutes before the transfusion and the other half when the transfusion is approximately one-half over. Packed, washed red cells or sedimented red cells are used for transfusion. In each of the patients described, this additional treatment enabled us to give the required amount of blood to a patient who was threatened with circulatory overloading.

Illustrative Case Histories

Case 1. D. C., age 64, a hypertensive patient for many years, was seen in the office with complaints of headache and morning nausea and vomiting. The blood pressure was 210/110, the heart was enlarged, and there was pallor of the skin and mucous membranes. Urine examination revealed a specific gravity of 1.006, 3+ albumin, a few red blood cells and a few hyaline casts in the sediment. The blood chemistry determinations were normal except for a urea nitrogen value of 60 mg/100 cc and a creatinine value of 2.4 mg/100 cc. The red blood count was 2.2 million and the hemoglobin was 9 g. An eye ground examination showed a few hemorrhages in each fundus.

The patient was placed on a low-protein diet with added vitamins and large quantities of iron. A gastrointestinal x-ray series was entirely negative except for thickening of the rugae in the stomach. The patient did not respond to home care with any significant degree of improvement, so he was hospitalized.

On the day after admission, a transfusion of 500 cc of whole blood was given slowly. Following the transfusion, it was later determined that the patient coughed for ten minutes but this was not reported. A transfusion of 500 cc of whole blood was started the next day. When about 200 cc were infused, the patient became dyspneic and cyanotic. Loud rales were heard over the entire chest. The patient had developed pulmonary edema due to circulatory overload and the transfusion was stopped. Morphine, atropine, cedilanid intravenously, Mercuhydrin®, oxygen under high pressure and finally phlebotomy were successively tried without avail. The patient died within 50 minutes.

Case 2. H. B. age 68, male, a known nephritic patient of several years' duration demonstrated the following clinical findings: Blood pressure 168/100, pallor, moderately enlarged heart, slight edema of the legs. Blood chemistry findings showed gradually increasing urea nitrogen levels which ranged from 52 mg/100 cc to 90 mg/100 cc of blood. The hemoglobin and red cell levels ranged from 9 to 7.5 g and from 3.6 million to 2.4 million, respectively. Treatment at home proved unsuccessful, so the patient was hospitalized.

The patient developed acute pulmonary edema while receiving one unit of washed red cells. Through heroic efforts, including several injections of morphine and atropine, cedilanid, oxygen and phlebotomy, the patient

improved over the ensuing 12-hour period. He refused further transfusion therapy.

He was subsequently hospitalized at another hospital where he died. He had received a blood transfusion, but it could not be determined whether this was a factor in his death. According to the patient's wife, he developed severe cough and dyspnea at the end of the transfusion, and died about two hours later in spite of heroic efforts to save him.

Comment: Both of the patients described above had chronic anemia due to uremia. Transfusions must be given with great caution in this type of patient. Unfortunately, the connection between transfusions and the patients' demise is often not recognized in case reports found in the literature.

CASE 3. A. B., female, age 69, was admitted to the Swedish Hospital on May 29, 1957 and discharged on June 19, 1957. She stated that for the previous four days she had been passing loose, jet black, foul-smelling stools accompanied by weakness and dizziness.

In 1954, she was hospitalized elsewhere for complaints of dyspnea, orthopnea, and edema of the legs. She was a known hypertensive patient. X-ray examination showed congestive changes at both lung bases and the electrocardiogram was consistent with posterior wall infarction. It was stated that her hemoglobin at this time was 8 g, but this was not explained further. The patient was given anticoagulants, digitalis and was discharged improved.

About four months before her present admission (on January 31, 1957), she was admitted to another hospital for bleeding peptic ulcer, with symptoms of generalized weakness and the passage of many jet black tarry stools. She stated that for the preceding year she had epigastric pain relieved by food. On admission to this hospital, her pulse was 100, she was pale and had engorgement of her neck veins. The heart was enlarged. Her blood count was 5.5 g of hemoglobin with 1.6 million red blood cells per cu mm. Her stool was strongly positive for occult blood. The patient had seven transfusions, and developed frank pulmonary edema after three of these. She required aminophyllin, mercuhydrin, and morphine sulfate on each occasion. A gastrointestinal x-ray series showed a constant deformity of the first portion of the duodenum without a definite ulcer niche. The interpretation was duodenal scarring secondary to a duodenal ulcer. The patient was discharged with a hemoglobin level of 11.5 g.

Four days before the present admission (May 29, 1957) the patient started to pass loose, jet black stools and developed generalized weakness. On admission the patient appeared pale and anxious, with distention of the neck veins. The hemoglobin was 7.6 g with 2.92 million red blood cells. Digitalis was continued and a mercurial injection was given. On May 30, 1957, she was given a packed red cell transfusion of 250 cc at a very slow rate. Following this, she developed frank pulmonary edema associated with extreme dyspnea and cyanosis. She received aminophyllin, mercuhydrin, morphine, and atropine and oxygen. The morphine and atropine had to be repeated three times during the ensuing two days before her chest became clear to auscultation. Phlebotomy was not done because the patient was markedly apprehensive and still anemic.

On June 1, it was decided to start Imferon, 5 cc daily intramuscularly. However, on June 4, because of a steadily falling hemoglobin level (5.75 g) it was decided to give packed cell transfusion by a modified method.

A hypodermic of morphine sulfate (gr $^1/_4$) and atropine sulfate (gr $^1/_{150}$) was prepared and half of this amount was given five minutes before the start of the transfusion and the other half was given about midway through the transfusion. In this manner, seven transfusions of packed cells were given without mishap of any type. The hemoglobin level on June 14 was 14.15 g with 4.87 million red blood cells.

On June 14, a gastrointestinal x-ray series revealed a persistent spasm of the duodenum, with a slight five-hour gastric residue. The patient was discharged improved on June 19, 1957.

CASE 4. C. B., female, age 72, was admitted to the Swedish Hospital on Sept. 1, 1957. The patient had a large esophageal hiatus hernia, which ulcerated and resulted in a large blood loss. In addition, she was treated periodically for arteriosclerotic heart disease, chronic myocardial failure, and heart block (2:1 heart block). On admission the hemoglobin level was 7.2 g with 3.6 million red blood cells. The heart was enlarged, the blood pressure was 160/110 and there were a few rales at both bases. The legs were not edematous and the liver was not enlarged. There was slight distention of the cervical veins. The Decholin® circulation time was 14 sec. The patient had been kept under control with weekly injections of a mercurial diuretic.

On the day of admission, a transfusion of 250 cc of washed, packed red cells was given by slow, intravenous drip. Frank pulmonary edema was precipitated before the transfusion was finished. Aminophyllin, mercuhydrin, oxygen, morphine sulfate, and atropine sulfate were required to treat this attack.

On September 4, another transfusion of 250 cc of washed, packed red cells was given, preceded by one-half of the morphine sulfate and atropine sulfate injection, exactly as in case 3. The other half was given during the transfusion, at a point when about one-half of the transfusion had been given. Thereafter, one additional unit of washed packed red cells was given daily for the ensuing six days, preceded and accompanied by the morphine and atropine injections as detailed above. These were all received by the patient without incident. At discharge, the hemoglobin level was 12.2 g with 4.0 million red blood cells.

Comment: In both case 3 and case 4, it was possible to give the required amount of blood to

patients in chronic heart failure with very little cardiac reserve by the simple expedient of giving the prophylactic injections of morphine and atropine as described in this paper. Subsequently, we have used this method many times with salutary effects in every patient in which it was tried.

Discussion

The number of actual published instances of circulatory overloading following transfusion is few. Plummer[11] reported five deaths from this cause, and Pygott[12] and DeGowin[13] each describe two fatalities. Drummond[14a] reported five deaths from pulmonary edema following transfusion. Reports of fatalities are no indication of the actual incidence of this complication, since many patients recover if the situation is recognized early and intensively treated.

There are several disorders in which it is relatively easy to produce pulmonary edema following transfusion.[9] Patients with heart disease, especially those with left ventricular strain, and patients with chronic anemia are the most likely subjects. Prolonged fevers, such as typhoid fever, or even a simple febrile reaction can place a burden on the circulation. Patients with pulmonary diseases, either acute or chronic lung infection, chest injuries and pneumothorax are predisposed to this complication of transfusion.

The effect of rapid intravenous infusions in normal individuals is well documented.[14b] Following such infusions the venous pressure rises, the heart becomes dilated, and much of the infused fluid remains for a time in the pulmonary vessels.[15,16] The experiments cited were with saline infusions, but even more pronounced effects would undoubtedly follow blood transfusions. The effect could well prove disastrous in organic heart disease, especially stenotic lesions of mitral and aortic valves and patients with borderline compensation.

In prolonged fevers, anemia is often combined with a toxic myocarditis. The presence of lung disease causes an additional right heart strain, so that circulatory overloading can occur more easily.

Circulatory Changes in Chronic Anemia: There are various circulatory changes in chronic anemia that are of considerable importance if transfusions are being planned as part of the treatment. The total circulating blood volume is reduced.[17] This reduction has been variously estimated to be from 14 to 33 per cent below normal, depending, of course, on the degree of anemia.[18] The reduction of the blood volume is apparently proportionate to the reduction of hemoglobin and is not dependent on the cause of anemia. The cardiac output is increased,[19] also depending on the reduction of hemoglobin, and has been said to average a 50 per cent increase. Brannon *et al.*[20] found that 7 g of hemoglobin per 100 cc was the critical level, above which no change in cardiac output was noted, while below this level there was a large increase in cardiac output.

Although some authorities[20,22] have reported normal venous pressure and normal right atrial pressures, others[21] have found higher values than normal. Scott,[9] writing in the Keynes' manual on blood transfusion, states dogmatically that there can be no reasonable doubt that the venous pressure, and presumably also the right atrial pressure, is raised in many cases of severe chronic anemia. This statement is based largely on the clinical finding of cervical venous distention in many cases of severe chronic anemia.

Prevention of Overload During Transfusion

Rate of Infusion: In chronic anemia, the transfusion must be administered by the slow-drip method, at a rate not exceeding 2 cc/kg body weight/hour, and if the anemia is severe, only 1 cc/kg/hour would be a safer rate of infusion. Scott[9] states that a constant watch should be kept for increasing distention of the cervical veins, and the transfusion should be stopped immediately if this occurs.

Digitalis: In an attempt to lower the risk of circulatory overload in chronic anemic patients, Sharpey-Schafer[6] recommends that the transfusion be carried out in the reclining position, because this reduces the pressure in the right atrium. McMichael and Sharpey-Schafer[8] noted that digoxin also lowers the right atrial pressure, and Scott[9] believes that an intravenous injection of 1.0 to 1.5 mg of digoxin immediately before transfusion is a rational procedure.

Luisada and Cardi,[23] however, caution against

rapid digitalization in patients with mitral stenosis. They state that in these patients the elevated pulmonary pressure is caused by a high right ventricular output in the presence of mitral obstruction. Rapid digitalization may precipitate pulmonary edema by increasing the right ventricular output while the outflow from the lungs is impeded by the mitral block. In one such instance, morphine and venesection lowered the pulmonary pressure and cleared the pulmonary edema.

Morphine: The empirical use of morphine and atropine in the treatment of pulmonary edema has been known for decades. Although the evidence for the use of morphine rests on fairly solid ground, the evidence for the use of atropine is more tenuous.

Morphine terminates most of the mild and some of the severe attacks of pulmonary edema, especially when associated with hypertension, uremia, coronary thrombosis, or mitral stenosis.[23] Morphine must be used with great circumspection, if at all, in patients with cerebral vascular disease or chronic cor pulmonale. The mechanism of action of morphine is not entirely known. It depresses the respiratory center and decreases the suction effect of dyspnea.[23] It has been stated that in pharmacologic doses, morphine causes no apparent change in cardiovascular dynamics.[24] Pulmonary atrial pressures in cardiac patients studied by catheterization decreased in 26 of 34 patients, but there was an increase in the pressure in eight patients.[25] In coronary patients, morphine may act by alleviation of anxiety and by interruption of harmful reflexes. Morphine decreases the basal metabolic rate, and thus could conceivably reduce the work of the heart and possibly also the venous pressure.[23] In any event, morphine is probably one of the most effective drugs in the treatment of pulmonary edema, even though we may not know exactly how it acts.

Atropine: The value of atropine in acute pulmonary edema is questioned by some experts, even though it has been found of value clinically. Its use was first reported[26] from England in 1927, but its beneficial effect was known many years earlier. Luisada and Cardi[23] believe that the drying effect of atropine on secretions and the results obtained in bronchial asthma were responsible for its use in pulmonary edema. There is another possibility, however, that these authors do not stress in their excellent review.

Antonini and Biancalani[27] reported patients with traumatic injury to the brain and spinal cord, in whom severe pulmonary edema occurred. In these instances, the pulmonary edema was thought to be due to pulmonary transudation because of direct neurogenic vasodilatation of the pulmonary vessels. It has been noted[28] that pulmonary edema can occur in nervous illness in which autonomic imbalance may play a part. Cooke[29] reported on the development of pulmonary edema in a healthy patient with ureteral colic who had been given eserine. Likewise, two patients with multiple sclerosis who were being treated with neostigmine developed attacks of pulmonary edema.[30] Paine, Smith, and Howard,[28] after a review of these instances, state that serious physiologic disturbances may follow parasympathetic stimulation even from ordinary movements or mild reactions of apprehension. One of the most useful of the anticholinergic drugs is atropine. If parasympathetic stimulation, from whatever origin, can cause pulmonary transudation and finally pulmonary edema, atropine may help reverse the process. In practical use, also, morphine when used alone in patients with pulmonary edema, may induce dreaded nausea and vomiting, which may not occur if atropine is used with the morphine.

It would be unusual indeed, if so simple a prophylactic method for the prevention of circulatory overloading as we describe had not in fact been tried before. We did not find it mentioned in any of the literature on transfusions available to us. However, even if the method described in this article should not prove to be completely unique, we feel that it is still worth reporting, because an important hazard of transfusion is stressed. Many practitioners have developed a cavalier attitude toward this form of therapy.

Summary

It is stressed that circulatory overloading following transfusion is especially liable to occur in certain types of patients: heart disease patients especially with left ventricular strain, chronic

anemia patients, also those with prolonged fever, pulmonary diseases, either acute or chronic, and with chest injuries. Two fatalities from circulatory overloading are described. A method of prevention is detailed which consists of administering packed red cells and a prophylactic injection of morphine and atropine, before and during the transfusion.

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Case Reports

Absence of the Pulmonary Valve Associated with Ventricular Septal Defect*

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CONGENITAL bicuspid and quadricuspid pulmonary valves[1–8] have been described not rarely both as isolated lesions and in association with other congenital malformations. Bicuspid pulmonary valve has been a cause of pulmonary regurgitation, usually of benign nature. Congenital absence of the pulmonary valve leaflets with severe pulmonic regurgitation has been reported only by Lavenne[9] and by Campeau.[10] Lavenne's case was that of a 46-year-old man who had Eisenmenger's complex with cyanosis and who died in congestive failure. Campeau's case was similar to Lavenne's, a 32-year-old male who died in congestive failure with a myocardial infarction. Ehrenhaft[11] has reported a 14-year-old boy with completely absent pulmonary valve leaflets, observed during direct surgery. He proposed rheumatic fever or bacterial endocarditis as possible causes for this malformation.

Recently, an infant was observed who at autopsy was shown to have almost complete absence of the pulmonary valve leaflets in addition to a ventricular and an atrial septal defect. A clinical diagnosis was made of congenital deformity of the pulmonary valve with severe pulmonic regurgitation and defect of the interventricular septum. It is the purpose of this report to emphasize those clinical findings which were of aid in identifying this condition.

CASE HISTORY

LMW (444395), a five-week-old white male infant from Bristol, Connecticut,† was referred to the Grace-New Haven Community Hospital on March 14, 1956 for evaluation of recurrent heart failure.

The patient was the product of a full term pregnancy in which there was frequent nausea and vomiting in the first trimester but no complicating trauma, infection or vaginal bleeding. The mother, age 21, had one previous pregnancy: a daughter weighing 7 lb at birth, now 16 months old and well. The maternal grandfather had diabetes and the paternal grandmother had hypertension. On February 9, 1956 the patient, weighing 5 lb 13 oz, was born after a normal, spontaneous delivery. There was a loud systolic murmur immediately present. A wheeze was heard over the chest. The cry was weak, but there was no apparent cyanosis. The patient fed well on evaporated milk formula and was discharged home with the mother on the tenth day. At three weeks of age the patient was readmitted to Bristol Hospital because of increased wheezing, and within three days developed cyanosis and hepatomegaly. A systolic murmur well transmitted to the back, and a separate diastolic murmur not transmitted were heard over the left precordium. Chest roentgenogram showed slight right and left ventricular enlargement of the heart, increased pulmonary vascular markings, and a mass in the hilum of the right lung which was interpreted as being a possible aneurysmal dilatation of the right pulmonary artery. A subsequent film demonstrated another mass in the upper right area of the mediastinum. Electrocardiogram (leads I, II, III only) showed a normal axis. With the administration of oxygen and digitoxin the cyanosis cleared and the liver reduced in size. The respiration improved and the patient was able to return home. Digitoxin was maintained at 0.006 mg daily. Four days later the patient began to cry vigorously, then, with eyes rolled upward, became cyanotic for 15 to 20 minutes. This was followed by pallor and listlessness and a similar episode recurred the next day. During the next two days respirations became rapid and grunting, feeding was poor, and the liver again became enlarged.

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† Patient was referred by Dr. Arnold Becker of Bristol, Connecticut.

On admission rectal temperature was 37.1 °C, pulse 166, respiration 80 with marked expiratory grunt and slight inspiratory retraction. Blood pressure was 120/65 in each arm, weight 3,000 g, length 50 cm, head circumference 34 cm with normal fontanelles. The patient appeared to be normally developed and fairly well nourished. There was no evidence of dehydration but the complexion was pasty. There was no cyanosis or subcutaneous edema. There was no deformity of the chest wall. The point of maximum impulse was not visible but could be felt in the 5th left intercostal space just lateral to the midclavicular line. Percussion suggested slight enlargement of the heart. The 1st and 2nd heart sounds were of poor intensity with the pulmonary 2nd sound inaudible. A grade IV harsh, blowing systolic murmur was heard maximally along the lower left sternal border and was well transmitted to the neck and interscapular area. This was followed immediately by a higher pitched diastolic murmur heard best in the 2nd and 3rd left interspaces but transmitted along the left sternal border only and to the apex. Femoral and brachial pulses were well felt and were equal. The lungs were clear except for a persistent expiratory wheeze. A firm rounded liver edge was felt 5 cm below the left costal margin. The spleen was not felt. There were umbilical and right inguinal hernias, each 3 cm in diameter and easily reducible. The testes were in the scrotum, and the remainder of the physical examination was normal.

Laboratory findings showed hemoglobin 13.9 g/100 ml; WBC 8400, with 69 per cent polymorphonuclears, 28 per cent lymphocytes, 3 per cent monocytes. Urine albumin, sugar, and sediment were negative. Nose and throat cultures showed normal flora with a few colonies of pneumococci. ECG showed sinus rhythm with rate of 166, P-R interval 0.13 sec, QRS duration 0.06 sec, normal axis, vertical electrical position, and right ventricular hypertrophy (Fig. 1). Fluoroscopy of the chest showed an enlarged right ventricle and very strikingly enlarged and extremely pulsatile pulmonary vessels in the hilar regions of the right upper and lower lobes and the left upper lobe. The roentgenograms are reproduced in Figure 2.

During the four weeks of hospital life the patient developed more and more frequent episodes of cyanosis and dyspnea during which the heart rate fell to 40/min and respirations to 10–20/min. Initially the attacks lasted 3 to 5 minutes and were relieved by oxygen, but later apneic periods developed which were treated by manual artificial respiration and subcutaneous caffeine. The digitoxin was increased to 0.02 mg daily and for about two weeks the respirations between attacks improved and the liver reduced in size, although digitalis effect was not detectable by ECG. During the last week of life increasing periods of dyspnea were accompanied by moist rales throughout the lungs and were relieved only by small intramuscular doses of morphine. At this time earpiece oximetry showed 98 per cent oxygen saturation at rest, and 82 per cent saturation with dyspnea.

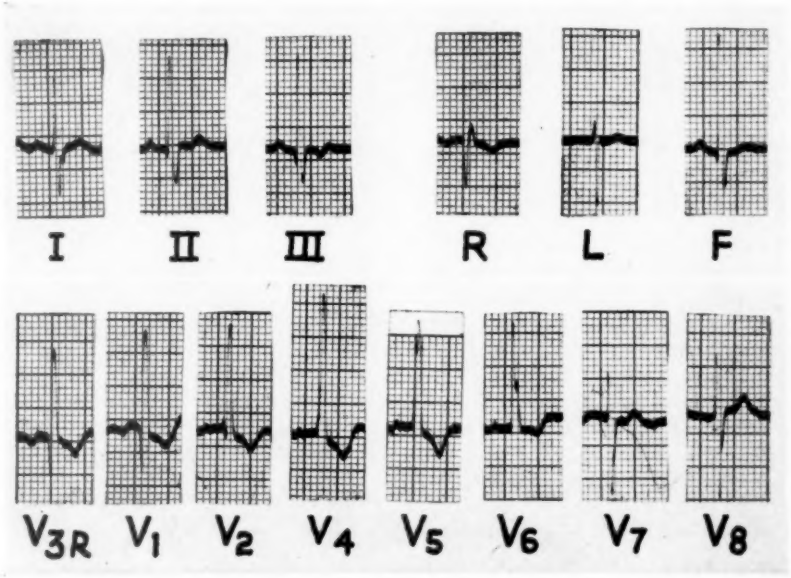

Fig. 1. Electrocardiogram showing right ventricular hypertrophy.

During the last 36 hours of the patient's life the heart rate gradually slowed, varying between 20–80 per min. Respirations fell to 20, then to 5 and finally to 1 or 2 per min until there was no longer a response to caffeine and the patient expired on April 11.

The antemortem diagnosis was large interventricular septal defect, possible atrial septal defect and congenital defect of the pulmonary valve with pulmonic regurgitation.

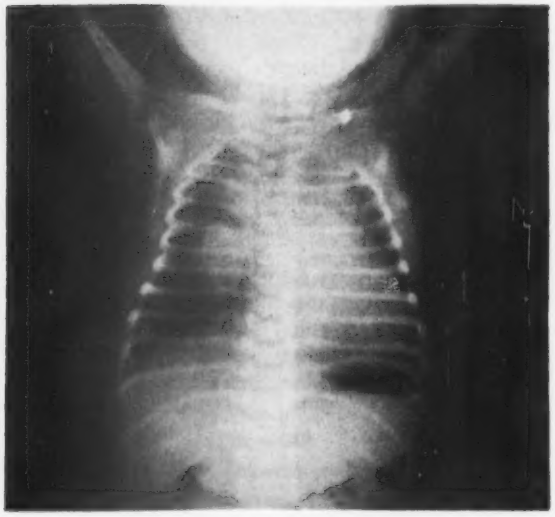

Fig. 2. Posteroanterior roentgenogram showing right ventricular hypertrophy and enlarged pulmonary vessels.

Autopsy Findings

At autopsy there was no excess fluid in the pericardial, pleural or peritoneal cavities. The pericardium was smooth and glistening. The great vessels were normal in position and course. The aorta was not enlarged. The pulmonary arteries were markedly dilated but there was a moderate degree of constriction and thickening at the level of the pulmonary valve ring. The ligamentum arteriosum could not be identified, nor were there openings into the aorta or pulmonary arteries at the expected site. There was a large bronchial artery arising from the upper surface of the aorta between the innominate and left common carotid arteries which descended posteriorly to the anterior surface of the trachea and right main bronchus. The heart appeared greatly enlarged due to a prominent right ventricle. The weight was not obtained as the lungs were not removed from the specimen. The epicardium was smooth and the myocardium was reddish-brown and resilient. The right ventricular wall measured 1.2 cm in thickness with marked hypertrophy of the trabeculae. The left ventricular wall measured 0.4 cm. The endocardium was smooth and shining throughout. The chambers of the right atrium and ventricle were markedly dilated. There was a large defect high in the interventricular septum with the aortic valve orifice overriding both ventricular cavities. The foramen ovale measured 1.5 cm in diameter and was incompletely covered by a thin membrane leaving an opening about 0.4 cm in diameter. The tricuspid, mitral and aortic valves were not remarkable with ring circumferences estimated to be, in order, 2.8, 2.6, 1.5 cm, respectively. The pulmonary ring circumference measured 1.5 cm. The pulmonary valve leaflets were absent (Fig. 3) and were replaced by a slight, irregular thickening which microscopically appeared to be fibrous tissue.

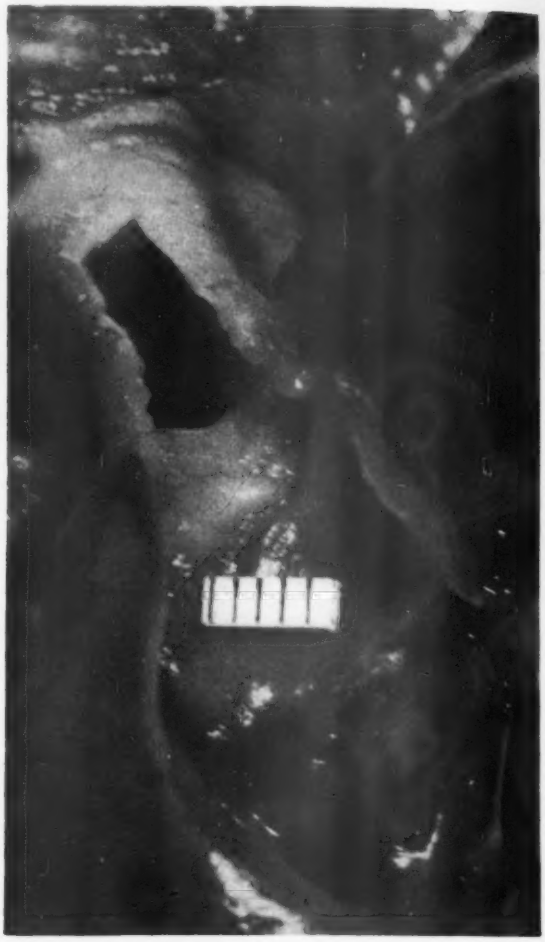

Fig. 3. Anterior view of the pulmonary valve orifice and outflow tract of the right ventricle (scale divisions = 1 mm).

There were no other abnormalities found except for marked congestion of lungs and liver, and the umbilical and right inguinal hernias. Abnormal changes in the media or intima of the pulmonary arterioles were not noted.

The pathologic diagnoses were summarized as follows:

(1) Hypoplasia of the pulmonary valve leaflets.
(2) Interventricular septal defect (high, large).
(3) Patent foramen ovale.
(4) Hypertrophy and dilatation of the right ventricle (marked) and right atrium (moderate).
(5) Congestion of lungs and liver (marked).
(6) Hernia of umbilicus and right inguinal canal.
(7) Aplasia of ductus arteriosus.

Discussion

This patient resembled those of Lavenne and Campeau who were acyanotic during infancy, showed similar cardiac murmurs, x-ray and electrocardiographic findings, and died in right sided cardiac decompensation. Both Lavenne's and Campeau's patients showed very extensive medial proliferative and fibrotic changes in the pulmonary arterioles. The latter findings were not present in our patient but might be expected to have developed with time in a patient with such a large ventricular septal defect.[12] The late cyanosis which Lavenne believed was associated with cardiac decompensation and venous stasis probably was related to these very extensive pulmonary arteriolar changes with the associated pulmonary hypertension augmenting the right to left shunting of blood through the ventricular septal defect. The pulmonary valves were very similar in the three cases. The patient presented showed a largely patent foramen ovale and a completely absent ligamentum arteriosum.

Ventricular septal defect by itself or combined with atrial septal defect may be a threat to the life of an infant.[13,14] The additional pulmonic regurgitation in this patient probably contributed to the early death.

Hemodynamic Effects of Pulmonary Regurgitation

Barger[15] studied three dogs who had pulmonary regurgitation produced by blind valvulotomy. These animals showed no changes in venous pressure even when subjected to very hard exercise on a treadmill. The dogs of Spencer[16] and Shaw[17] which had only one valve cusp incised were not severely incapacitated. However, when Kay[18] removed all three pulmonic cusps, ten of the fifteen dogs developed systolic pressures of over 50 mm Hg and three dogs developed pressures of over 90 mm Hg in the right ventricle. One dog died eight months postoperatively in right sided cardiac decompensation even though it was never allowed to exercise vigorously. The diastolic pressure in the pulmonary artery was greater than that in the right ventricle in 13 of the 15 animals. The systolic pressure in the pulmonary artery was elevated but less than the systolic pressure in the right ventricle in 12 of 15 dogs.

Campeau's patient revealed a pulmonary artery pressure of 180/23–28 mm Hg and a right ventricular pressure of 180/0. There was absence of the incisural notch in the pulmonary artery pressure curve. The systolic pressures, greatly higher than those observed in dogs, may have developed as a result of long standing disease.

Ford[19] has obtained accurate pressure curves from a patient proven to have had a bicuspid pulmonic valve as an isolated lesion. He observed a hesitation of the pulmonary arterial pressure rise similar to that observed by Wiggers in aortic insufficiency and believed to result from a pressure change as the mass of blood in the ventricle begins to accelerate. The duration of systole in the cardiac cycle was increased.

From this physiologic evidence, we can conclude that the severity of the changes in cardiac capacity are related to the extent of the insufficiency of the pulmonary valve and that cardiac decompensation might develop from severe pulmonic regurgitation alone.

Clinical Features of Pulmonary Regurgitation

The clinical features that suggested pulmonary insufficiency were (1) hyperactive pulmonary artery pulsations and (2) characteristic early diastolic murmur in the pulmonic area; (3) the inaudible pulmonary second sound led to the conclusion that the insufficiency was caused by an anomalous valve.

(1) *Hyperactive Pulmonary Artery Pulsations:* Although hilar expansile pulsations of the pulmonary arteries are observed by fluoroscopy in a variety of congenital cardiac conditions, particularly those involving left to right shunts, the degree of pulsation observed in this patient was extreme. Also, the aneurysmal dilatation of the pulmonary artery far exceeded that observed in infants with solely left to right cardiac shunts. This severe pulmonary artery pulsation was very reminiscent of the great expansion and collapse of the aorta seen in patients with severe aortic regurgitation. Heyer[20] has recorded electrokymograms of the pulmonary

artery in a case of "tetralogy of Fallot with pulmonic insufficiency." The absence of an incisural notch suggested that pulmonic regurgitation was present. This technique previously appeared to be definitive in determining aortic regurgitation and might be effectively employed to delineate pulmonic regurgitation.

(2) *Characteristic Early Diastolic Murmur in the Pulmonic Area:* The murmur of pulmonic regurgitation is said to differ from that of "relative pulmonic insufficiency" by being harsher and longer, as Luisada has shown by phonocardiography.[21] The diastolic murmur heard in our patient was harsher and more sustained than the early, high-pitched blowing diastolic murmurs observed not rarely in children with large left to right shunts which are presumably from "relative insufficiency." The diagnosis of left to right shunting of blood in this patient was apparent from the great blood flow through the lungs since even during diastole the pulmonary blood flow appeared greatly increased.

The systolic murmur was very prominent and suggested ventricular septal defect by its harshness and location.

(3) *Absence of the Pulmonary Second Sound:* In infants with ventricular or atrial septal defects with aneurysmal dilatation of the pulmonary artery and "relative pulmonic insufficiency" pulmonary hypertension is often present with increase in the intensity of P_2. In atrial septal defect without pulmonary hypertension the pulmonary second sound will be audible and split because of the unequal closure of the pulmonic and aortic valves. A soft P_2 should be heard in some patients with bicuspid pulmonic valves with pulmonic regurgitation. However, the complete absence of the pulmonary second sound caused us to suspect a more severe anatomical anomaly.

Cardiac catheterization was deferred in the hope that medical management might improve our patient so that this study could be tolerated. The episodes of bradycardia and dyspnea this patient showed were very similar to those observed in patients with severe pulmonary hypertension. The infant's heart rate slowed progressively over a period of several hours before death ensued.

One can speculate that surgical closure of the ventricular septal defect could have improved this child, but it is most unlikely that he would have survived major surgery.

Summary

(1) A case of congenital absent pulmonic valve with ventricular septal defect in a five-week-old male is presented.

(2) The clinical findings of this patient, suggesting severe pulmonic regurgitation and ventricular septal defect, are discussed in order to define diagnostic criteria for this malformation.

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Coarctation of the Aorta with Patent Ductus Arteriosus and Multiple Intracardiac Defects*

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IT IS well recognized that when coarctation of the aorta is associated with cardiac failure in infants and young children, the prognosis is extremely grave and other congenital cardiovascular anomalies are almost invariably present. The following report of a case of this type shows several points of interest, in that (1) the patient survived, in reasonably good health, to the age of five years; (2) difficulty was experienced in making an anatomic diagnosis during life due to the severe degree of pulmonary hypertension present; (3) numerous congenital cardiac anomalies were found at autopsy; and (4) histology of the pulmonary vessels showed well-developed changes of pulmonary hypertension.

CASE REPORT

This little girl was five years and two months of age when she died. She was first seen at the age of one month because of edema of the legs and hands. Her mother had noticed that at times the feet were blue, and it was observed by the examining physician that generalized cyanosis occurred when the child cried. She gradually improved and continued to grow slowly. When two years old, she weighed only 18 pounds (birth weight 5 pounds) and this retardation of physical development continued until her death. Mental progress was normal, however, and she was physically active. She walked when 18 months old and at the age of four years she could walk a mile on level ground and mount stairs without apparent effort.

On three occasions between the ages of six months and two years, cyanotic attacks terminating in convulsions occurred. On examination when she was two years old it was noticed that the pulmonary 2nd sound was very loud.

When three and one-half years of age her mother noticed bloodstaining around the child's mouth and on her pillow on waking over a period of two weeks, but frank hemoptysis did not occur. When four years of age it was observed that the femoral pulses were present and of good volume, and that the brachial blood pressure was 110/80.

At the age of five years and two months she was admitted for special investigation with a provisional diagnosis of severe pulmonary hypertension, probably secondary to a congenital cardiac anomaly such as a septal defect.

On examination she was a small, thin child with slight central cyanosis equal in both the upper and lower extremities. No clubbing of the fingers or toes was present.

Cardiovascular system: pulse 120/minute, brachial blood pressure 110/80, femoral pulses were present and of good volume. The apex beat was in the anterior axillary line. A heaving right ventricular impulse was felt to the left of the sternum and up into the left 2nd and 3rd intercostal spaces. The 2nd sound was palpable in the pulmonary area. No bruits were heard but the second sound at the base of the heart was closely split with a very loud second element.

Examination of the other systems revealed no abnormality.

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INVESTIGATIONS

Electrocardiogram: The record showed evidence of gross right ventricular hypertrophy.

Chest Radiogram (Fig. 1): There was moderate cardiac enlargement with marked prominence of the main pulmonary artery. The aortic knuckle could not be identified. The hilar vessels were enlarged and the appearances were those of pulmonary plethora. There was no peripheral vascular narrowing.

Cardiac Catheterization: The intracardiac pressures were recorded and blood samples taken:

Pressures

Site	mm/Hg
Right atrium	12/0
Right ventricle	94/0
Main pulmonary artery	112/65
Right pulmonary artery	97/53

Oxygen saturations

Site	O_2 content (vol %)	% saturation
I.V.C.	12.25	62.4
S.V.C.	11.9	60.7
R.A. (high)	13.5	68.8
R.A. (low)	13.38	68.2
R.V. (high)	13.42	68.4
R.V. (low)	13.42	68.4
R.V. (outflow tract)	15.18	77.3
R. pulm. artery	14.75	75.1
O_2 capacity	19.65	

No arterial sample was obtained.

An hour after cardiac catheterization the child suddenly collapsed with cardiac arrest. Cardiac massage was begun through the left 4th intercostal space and spontaneous beating became established. An hour afterwards, however, the heart stopped again and could not be restarted.

AUTOPSY FINDINGS

External Appearances: A small, thin child with a recent thoracotomy incision. No clubbing of fingers or toes.

Cardiovascular System: The heart was enlarged and weighed 140 g. The wall of the right auricle was hypertrophied (0.4 cm thick) and showed pronounced trabeculation. The right ventricular wall was 1.2 cm thick (Fig. 2) and again showed marked trabeculation. The

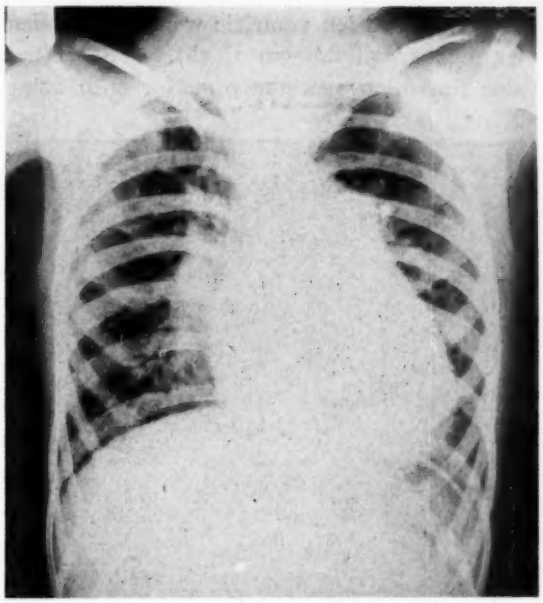

Fig. 1. Chest x-ray showing cardiac enlargement, marked prominence of the main pulmonary artery and pulmonary plethora.

Fig. 2. External appearance of heart showing grossly enlarged main pulmonary artery, ductus arteriosus, position of coarctation, and hypoplastic aortic arch. Gross right ventricular hypertrophy is apparent.

left auricle and left ventricle were normal (left ventricular wall 0.5 cm thick). The mitral valve was abnormal, the posterior cusp being very rudimentary. The tricuspid valve was normal. The pulmonary valve had three cusps and appeared to be competent, although the valve ring was increased in diameter. The aortic valve was bicuspid and the valve ring appeared small.

Fig. 3. Large interventricular septal defect in position of membranous septum.

The interventricular septum was thickened by muscular hypertrophy. There was no membranous septum and the ventricles communicated via a large defect measuring 1.3 x 1.2 cm (Fig. 3).

The interauricular septum was represented by a thin fibrous membrane with a number of fenestrations and a large anterior defect (Fig. 4). Fibrous tags were present on the posterior margin. The appearances were those of an unsupported septum primum, the only evidence of a septum secundum being a rudimentary crescentric muscular ridge in the postero-inferior wall of the right auricle adjacent to the fenestrated membrane.

The superior and inferior venae cavae entered the right auricle, and the pulmonary veins, the left auricle. There was no anomalous venous drainage.

The main pulmonary artery was grossly enlarged (2.1 cm diameter), and from its point of bifurcation into right and left pulmonary arteries a large patent ductus arteriosus (0.8 cm

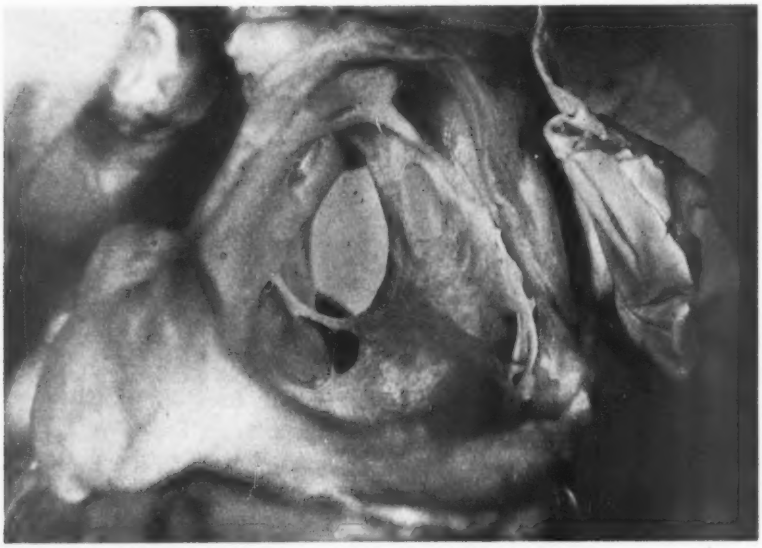

Fig. 4. Interauricular septum viewed from left auricle showing fenestrations and large anterior defect. (Left of figure.)

diameter) continued directly into the descending aorta (Fig. 5).

The aorta was hypoplastic and measured only 1.0 cm in diameter in its ascending portion. Immediately distal to the origin of the innominate artery the arch became much narrower, gave rise to the left common carotid and left subclavian arteries and then joined the junction of ductus arteriosus and descending aorta. A complete coarctation was present at this point (Fig. 5). There was no evidence of collateral channels. The aortic isthmus measured only 0.3 cm immediately proximal to the coarctation and the descending aorta immediately distal to the ductus arteriosus measured 1.0 cm diameter.

Respiratory System: Some collapse of the left lung was present (caused by displacement during cardiac massage). No other external abnormality was seen. There was no evidence of pulmonary edema.

The digestive, nervous, urogenital, and endocrine systems showed no abnormality.

Histology of the Lungs: Blocks were taken from all lobes of both lungs and from each block two sections were cut. One was stained with hematoxylin and eosin and the other with Weigert's elastic stain, counterstained with Van Gieson. Pulmonary arterial branches of all sizes from 50 μ to over 1,000 μ in diameter were examined in each section. All these vessels showed abnormal histologic appearances. Muscular hypertrophy of the media, increase in the amount of elastic tissue and thickening of the elastic laminae, intimal hyperplasia and increase in thickness of the adventitial coat were all seen in varying degree.

The arterioles (diameter 50–100 μ) and small muscular arteries (100–300 μ diameter) showed conspicuous hypertrophy of the muscular media and concentric thickening of the intima (Fig. 6). The larger muscular arteries (300–1,000 μ) showed in addition focal intimal thickening overlying points of disruption of the internal elastic lamina. Occasional aneurysmal dilatations were observed arising from the muscular arteries and occasional organized thrombi were encountered. The elastic arteries (over 1,000 μ diameter) showed increased amounts of elastic tissue in their walls but there was no evidence of atheroma of these vessels.

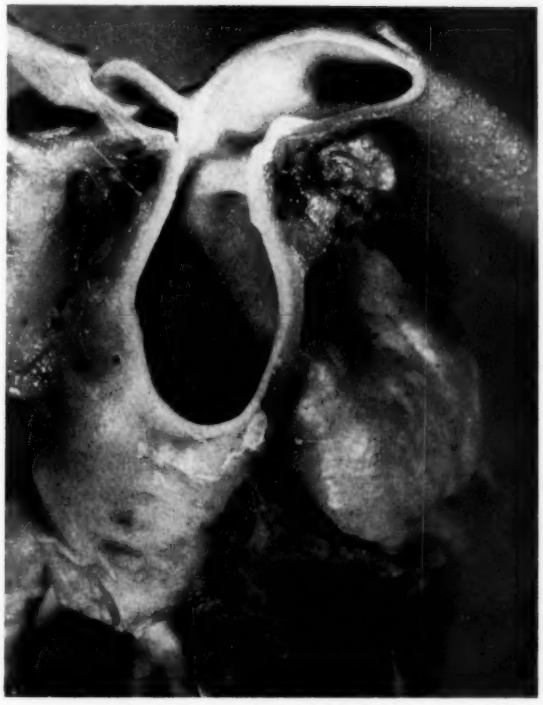

Fig. 5. Showing widely patent ductus arteriosus continuous with descending aorta. Complete coarctation at junction of aortic arch and ductus arteriosus.

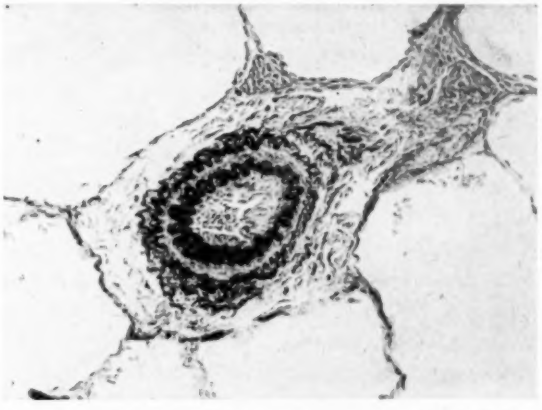

Fig. 6. Small muscular artery showing thickening of elastic laminae, intimal hyperplasia, and some adventitial thickening. (Weigert's elastic stain and Van Gieson, × 250.)

The interstitial tissues of the lungs and respiratory passages appeared normal.

Discussion

Clinical Features: At the age of one month this child developed congestive heart failure and it seems likely that the severe degree of pul-

monary hypertension found later was present from birth.

From the anatomic findings it is difficult to see how the flow of blood through the patent ductus arteriosus could have been other than from pulmonary artery to descending aorta, yet apart from the early observation by the mother, differential cyanosis was not seen. From the oxygen saturations obtained during cardiac catheterization it appears that the intracardiac shunts both at ventricular and auricular levels were from left to right, thereby considerably increasing the oxygen saturation of pulmonary arterial blood. The x-ray evidence of pulmonary plethora supports this view. Thus, blood passing through the ductus arteriosus into the descending aorta need not produce noticeable cyanosis of the lower limbs. On exertion, however, slight further rise in pulmonary arterial pressure must have been sufficient to reverse either one or both of the intracardiac shunts. The cyanosis then seen was marked and was present in both upper and lower parts of the body. When cyanosis was observed in this child it was always generalized.

Comparison with Other Cases: Maude Abbott[1] in her analysis of 1,000 cases of congenital heart disease records 9 patients with "infantile coarctation" and 6 others in whom the pulmonary artery formed the descending aorta. A variety of other lesions was present in these cases, including patent ductus arteriosus, atrial septal defect and interventricular septal defect, but it is not clear how many of these lesions coexisted in any single patient. Of all these 15 patients, however, the oldest survivor died at the age of nine months.

Edwards *et al.*[2] discuss the findings in four cases with coarctation of the aorta and patent ductus arteriosus, and their case 3 is in many ways similar to the one presented here. Generalized cyanosis occurred terminally in their case which died in heart failure at the age of 23 months. At autopsy an incomplete coarctation of the aorta was present, the ductus arteriosus was patent, and there was a defect of the membranous part of the interventricular septum. The foramen ovale was patent and the aortic valve bicuspid.

Seaman and Goldring[3] in their review of 12 cases of coarctation of the aorta with patent ductus arteriosus in which the diagnosis had been proved either surgically or at autopsy describe one child (case 3) dying at the age of three months in whom generalized cyanosis was a feature. A defect in the membranous part of the interventricular septum and a patent foramen ovale were found in this case at autopsy.

It appears, therefore, that children with coarctation of the aorta and patent ductus arteriosus but no collateral circulation may owe their limited survival to intracardiac shunts which indirectly increase the systemic oxygen saturation. Pulmonary hypertension would seem to be an essential feature of cases of this type.

Summary

A case is presented of coarctation of the aorta with patent ductus arteriosus and multiple intracardiac defects in a child surviving until the age of five years. It is considered that the relatively long survival was due in large measure to the presence of left to right shunts at both atrial and ventricular levels.

Acknowledgments

We are indebted to Dr. E. C. Allibone and to Mr. G. Wooler for permission to publish this case, to Mr. N. C. England for the photomicrographs, and to Mr. D. Coulson for the histologic preparations.

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Historical Milestones

Ascites as Described by Aulus Cornelius Celsus (ca. A.D. 30)

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AT THE PRESENT time problems of fluid balance are very much to the fore in cardiologic circles and supply the theme of countless articles and innumerable staff-room discussions. Although the combat between proponents of "forward failure" and defenders of "backward failure" is beginning to abate, the problem of morbid effusions will always remain with us.

It is chastening to recognize that intelligent attacks on this problem existed even in antiquity. Aulus Cornelius Celsus, whose treatise *De Medicina* is quoted in the following excerpt, is thought to have been born about 25 B.C. He was a Roman encyclopedist; scholars have not been able to decide whether he was a physician or layman. His treatise on medicine was perhaps part of a larger work on various arts and sciences and was probably written in A.D. 30 or thereabouts. The excerpt is taken, with slight modification, from the translation by W. G. Spencer, published in the Loeb Classical Library.[1]

CELSUS ON EDEMA AND ASCITES

But a chronic malady may develop in those patients who suffer from a collection of water under the skin, unless this is dispersed within the first days. The Greeks call this hydrops. And of this there are three species: sometimes the belly being very tense, there is within a frequent noise from the movement of wind; sometimes the body is rendered uneven by swellings rising up here and there all over; sometimes the water is drawn all together within, and is moved with the movement of the body, so that its movement can be observed. The Greeks call the first tympanites, the second leukophlegmasia or hyposarca, the third ascites. The characteristic common to all three species is an excessive abundance of humor [fluid], owing to which in these patients ulcerations even do not readily heal. This is a malady which often begins of itself; often it supervenes upon a disease of long standing, upon quartan fever especially.* It is relieved more easily in slaves than in freemen, for since it demands hunger, thirst, and a thousand other troublesome treatments and prolonged endurance, it is easier to help those who are easily constrained than those who have an unserviceable freedom. But even those who are in subjection, if they cannot exercise complete self-control, are not brought back to health. Hence a not undistinguished physician, a pupil of Chrysippus, at the court of King Antigonus, held that a certain friend of the king, noted for intemperance, could not be cured, although but moderately affected by that malady; and when another physician, Philip of Epirus, promised that he would cure him, the pupil of Chrysippus replied that Philip was regarding the disease, he the patient's spirit. Nor was he mistaken. For although the patient was watched with the greatest diligence, not only by his physician but by the king as well, by devouring his poultices and by drinking his own urine, he hurried himself headlong to his end. At the beginning, however, cure is not

* Rome was highly malarious until very recent times. Malaria was also common among the Greeks, whose writings Celsus probably copied. The tendency of quartan malaria to become complicated by nephrosis is amply attested by modern experience.

difficult, if there is imposed upon the body thirst, rest, and abstinence; but if the malady has become of long standing, it is not dispersed except with great trouble. They say, however, that Metrodorus, a pupil of Epicurus, when afflicted with this disease, and unable to bear with equanimity the necessary thirst, after abstaining for a long while, was accustomed to drink and then to vomit. Now if what has been drunk is then returned, distress is much reduced; but if retained in the stomach, it increases the disorder; and so it must not be tried in every case. But if there is also fever, this is first of all to be overcome by the methods which have been prescribed, concerning possible relief in such cases. If the patient has become free from fever, then at length we must go on to those measures by which the disorder itself is usually treated. And here, whatever the species, so long as the disease has not taken too firm a hold, the same remedies are required. The patient should walk much, run a little, and his upper parts in particular are to be rubbed while he holds his breath. Sweating is also to be procured, not only by exercise, but also by heated sand, or in the sweating-room, or with a dry oven and suchlike; especially serviceable are the natural and dry sweating-places, such as we have in the myrtle groves above Baiae. The bath and moisture of every kind is wrong. Pills composed of wormwood two parts, myrrh one part, are given on an empty stomach. Food should be of the middle class indeed, but, of the harder kind; no more of drink is to be given than to sustain life, and the best is that which stimulates urine. But that, however, is better brought about by diet than by medicament. If, nevertheless, the matter is urgent, one of those drugs which are efficacious is to be made into a decoction, and that given as a draught. Now this faculty seems to belong to iris root, spikenard, saffron, cinnamon, cassia, myrrh, balsam, galbanum, ladanum, oenanthe, opopanax, cardamon, ebony, cypress seeds, the taminian grape which the Greeks call staphisagra, southernwood, rose leaves, sweet flag root, bitter almonds, goat's marjoram, styrax. . . . The mildest of these, however, are to be tried first, such as rose leaves or spikenard. A dry wine is beneficial, but it must be very thin. It is good besides to measure every day with string the circumference of the abdomen, and to put a mark where it surrounds the belly, then the day following to see whether the body is fuller or thinner, for the thinning shows a yielding to the treatment. Nor is it unserviceable to take the measure of his drink, and of his urine; for if more humor [fluid] is evacuated than taken in, then at last there is hope of recovery.

Comment

If Celsus had written this text for The American Journal of Cardiology the Editor would probably have required him to subjoin a summary, which might well have included the following noteworthy observations:

(1) Abdominal effusions may complicate long-standing diseases, especially quartan fever (malaria).

(2) Effusions are more easily treated in controllable patients such as slaves than in uncontrollable persons such as freemen.

(3) A case of ascites in an alcoholic nobleman proved incurable because the patient could not control his intake of fluids.

(4) The patient should drink only enough to sustain life.

(5) Diuretic drinks are the best.

(6) The circumference of the abdomen should be measured daily.

(7) The quantity of ingested fluid and the quantity of urine should be measured daily. This provides a clue as to the patient's progress.

Reference

1. Celsus De Medicina. With an English translation by W. G. Spencer. Cambridge, Harvard University Press; London, Wm. Heinemann, 1935–1938, 3 vols. See Book III, chap. 21 (vol. 1, pp. 313 ff.). Permission for publication is gratefully acknowledged.

Ventricular Tachycardia with Syncope

HISTORY

THE PATIENT, a 63-year-old white salesman, was admitted to the hospital one hour after the sudden onset of dizziness, profuse perspiration, and weakness, followed by loss of consciousness for about one minute. There were no convulsions. On admission, there was shortness of breath and nausea. The patient denied chest pain but complained of a "strange feeling" inside of his chest. Five years previously, the patient was treated for four weeks in a hospital because of an acute anteroseptal infarction, from which he recovered without complications. Three months prior to the recent episode, he experienced a minor "fainting spell."

PHYSICAL EXAMINATION

The patient was lying flat in bed and appeared acutely ill. The face was ashen-gray in color and the skin was moist and clammy. The blood pressure was 96/82 and the pulse, 170 and regular. The heart sounds were very loud and regular; there were no murmurs or friction rubs.

ELECTROCARDIOGRAPHIC FINDINGS

An electrocardiogram revealed ventricular tachycardia. While the tracing was recorded, the patient became unresponsive and shock developed. In the meantime, the electrocardiogram revealed the onset of ventricular tachycardia originating alternatively in the two ventricles (Fig. 1). Three hundred mg of procaine amide (Pronestyl®) were given intravenously in a few seconds, followed by slow intravenous injection of another 300 mg under continuous electrocardiographic recording. After the first injection, a pattern of ventricular tachycardia from a single focus was again noticed (rate = 162). The rate progressively slowed down while the ventricular complex gradually became normal. At this time, the blood pressure was 108/78 and the patient was again conscious and responsive.

DISCUSSION

The patient was put on a maintenance dose of quinidine and kept at bed rest. Follow-up studies (electrocardiograms, blood chemistry—

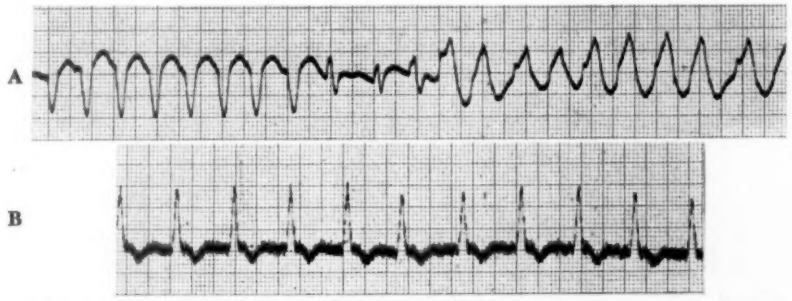

Fig. 1. Electrocardiograms in lead V-4. (A) During the attack showing biventricular tachycardia. (B) Soon after intravenous injection of procaine amide. The rate is 112/min and the ventricular complexes are normal except for the inverted T wave.

including transaminase level, and chest x-ray) failed to disclose a new infarction, an extension of the old one, or the existence of a myocardial aneurysm.

It is likely that acute coronary insufficiency precipitated the sequence: monoventricular ventricular tachycardia, then biventricular tachycardia, which is frequently followed by ventricular fibrillation. The prompt use of procaine amide led to resumption of sinus rhythm and saved the patient's life.

A. A. Luisada, M.D.
M. R. Testelli, M.D.
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Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

The Hyperventilation Syndrome

The tensions and uncertainties of today's living are responsible for an increasing amount of psychosomatic illness. Day-to-day frustrations produce anxiety, which is often manifested by hyperventilation. The importance of hyperventilation is that it can produce symptoms and signs which simulate organic heart disease.

Dr. Ellis P. Singer (Veterans Hospital, Bronx, New York) recently studied the clinical pictures resulting from hyperventilation secondary to anxiety. In an outpatient clinic of female dependents, 50 patients were studied, representing an incidence of 6.3 per cent of the total patient load.

The most common symptoms were: dizziness in 35 (5 patients had actual syncope), headache in 27, breathlessness in 24, chest pain or discomfort in 21, "nervousness" in 20, palpitation in 17, numbness and tingling in 12, and anorexia and/or nausea in 12. Less common manifestations were tinnitus, abdominal discomfort, choking, dysphagia, belching, and hot or cold flashes. The hyperventilation syndrome was considered responsible for the patient's symptoms when organic disease was not found by clinical or laboratory examination, and when 90 sec or less of forced overbreathing reproduced a major part or all of the patient's complaints.

The differential diagnosis of cardiac, pulmonary, neurologic or gastrointestinal conditions can be made by careful clinical and laboratory examinations. Dizziness and syncope due to postural hypotension can be ruled out by the occurrence of symptoms in the recumbent position. Absence of symptoms on careful carotid sinus pressure rules out a sensitive carotid sinus. Absence of any degree of heart block excludes Stokes-Adams attacks, which are rare in the younger age group. Petit mal, typically characterized by several momentary losses of consciousness per day, rarely has its onset after adolescence and can be excluded by an electroencephalogram. True vertigo, associated with various intracranial conditions, can be differentiated by the presence of other positive neurologic signs. Chest pain can mimic angina, but a painstaking history, with or without electrocardiographic confirmation, will establish this diagnosis. ECG changes, however, can occur with hyperventilation, and can cause inversion of T waves in the standard and precordial leads. (Dr. Singer believes that these are due to a vagal reflex arising in the thorax, similar to the Hering-Breuer reflex.) They could be blocked by potassium or parasympatholytic drugs. Breathlessness due to pulmonary disease can be distinguished by normal exercise tolerance, occurrence of symptoms at rest, and absence of orthopnea, rales, cyanosis, cough, sputum, or x-ray changes. Organic gastrointestinal diseases can be excluded by repeatedly normal x-ray examinations. The most difficult problem is to separate symptoms of hyperventilation from those due to organic disease where the two coexist. Careful evaluation is necessary here.

Therapy consisted mainly of reassurance and explanation of symptoms to the patient, rather than drug therapy. Simply holding one's breath for 20 to 30 sec at the first sign of an acute attack may abort the attack. Of course, the resolution of the underlying anxiety-producing situation through psychotherapy is the ultimate goal of therapy.

A Permanent Indwelling Heart Pump

At the meeting of the American Society for Artificial Organs in Philadelphia (April 14–18), Dr. B. K. Kusserow (Department of Pathology, Yale University) described a small implantable blood pump which can be used to substitute for the heart. The pump is only 7 in. long, $2^{3}/_{4}$ in. round, and consists basically of (1) a pump chamber and (2) an electromechanical, nonhydraulic drive mechanism. The pump is powered by a small alternating current motor. This is coupled to the pumping diaphragm by means of a special drive mechanism with a worm gear assembly for motor speed reduction and torque gain, and a small cam yoke assembly to convert the rotary motor motion to the type of motion needed for the pumping action.

Application to the Experimental Animal: The pump has been used to substitute partially for the work of the right heart only. Venous blood reached the pump through a cannula introduced into the inferior vena cava via a right auricular incision. Blood from the pump was returned to either the proximal or distal stump of the divided left pulmonary artery. The pump itself was placed in the abdomen, usually into the right abdominal gutter, through a mid-line incision. Both withdrawal and return cannulas entered the thorax via separate stab wounds in the anterior part of the diaphragm. The power cord, enclosed in a polyethylene tube, was brought out of the abdomen through a stab wound in the right flank, and plugged in an electric outlet. With the pump in such an intra-abdominal position, no sacrifice of pulmonary ventilatory function occurs. Adequate anticoagulation was achieved by giving heparin 1.0 to 1.5 mg/kg of body weight every 4 hr. To date, the longest period of uninterrupted intracorporeal pumping was $10^{1}/_{2}$ hours.

Tissue reactions observed at necropsy were (1) local hyperemia of the tissues about the pump site, and (2) some scattered subserosal mesenteric petechiae. Some fibrin deposit was encountered on the closing surface of the flap valves, but no emboli were grossly apparent in the lungs.

Did you know that . . .

Massive pulmonary embolism can simulate the clinical and electrocardiographic picture of acute posterior myocardial infarction. In both conditions, the patient may experience severe substernal pain. In addition, nausea and vomiting, pain in the abdomen, cyanosis, shock, and a Q_3 may be present. However, in massive pulmonary embolism, dilatation of the pulmonary artery occurs. This can be diagnosed by the presence of a forceful systolic pulsation which can be seen and felt in the second left interspace. In addition, a loud systolic pulmonary murmer may be present and even a rough friction rub over the pulmonary artery area. This probably occurs when the dilated pulmonary artery rubs against the pericardium.

In the electrocardiogram, massive pulmonary embolism causes signs of clockwise rotation to appear. These include a QR pattern in lead aVR and even in precordial lead V_1 or leads V_1-V_2. This pattern does not occur in posterior myocardial infarction.

* * *

Fever is common in patients with chronic left- or right-sided heart failure. It is due partly to the increased oxygen consumption which results from the dyspnea of left-sided heart failure, and as a result of decreased heat dissipation through the skin. The reason for this is that there is a decreased blood flow through the skin because of the decreased cardiac output. As a result, sweating is depressed.

It has been stated that when the temperature rises more than 1° in a patient with congestive heart failure, it is a sign of a complication, such as pulmonary infarction, active rheumatic fever, subacute bacterial endocarditis, phlebitis, etc. However, heart failure alone can cause fever as high as 102° for long periods. E.G.

Cardiac Resuscitation

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Doctrine of Hypoxia

Indoctrination is such a familiar term that one seldom considers that it implies a "doctrine."

A doctrine is described as "any body of teachings offered to others as true and practical." The only authority recognized in a doctrine, therefore, is its intrinsic truth and usefulness, i.e., the doctrine of States' Rights, doctrine of the law of gravitation, of abdominal surgery ("expose the field, remove foreign matter, apply treatment where it will do the most good"). The truth of a doctrine emerges after it has been proposed, kicked around for a long time, and has finally settled down as a useful starting point for some related idea.

THE DOCTRINE

Stages of Hypoxia: The "doctrine of hypoxia" consists of its recognized effects and the over-all methods of treatment. These effects, or stages of hypoxia, from onset to termination (irreversible cardiac arrest), were proposed by the Committee on Asphyxia of the American Medical Association in 1938. A questionnaire stressing the stages of asphyxia was mailed to the heads of every obstetrical department of every university in the United States and Canada. Forty-eight of the 63 who replied specifically approved the outline of the stages of asphyxia proposed, namely, depression, spasticity, flaccidity. For example, "thoroughly in accord," Pennsylvania; "simple, sane, conservative," Georgia; "seems extremely sound," Georgia; "meets in every detail with observation and treatment carried out in our institutions," Louisiana; "accepted principles urgently necessary," Nebraska; "simple and very rational classification, I like it," Canada. (See *Art of Resuscitation*, Reinhold Pub. Co., N. Y., p. 414.) These stages of asphyxia have been taught as true and practical in all courses presented by the National Resuscitation Society from 1947 through 1958. They have been presented at panels in cooperation with the Armed Services, Honolulu, in January, 1949, and at Atlantic City in 1952. They have formed part of the exhibits at the Annual Meeting of the Association of American Medical Colleges, at Colorado Springs, Atlantic City, French Lick Springs, and Swampscott, Mass. In April, 1955, they were presented for the consideration of each of the ten specialty board chairmen of the A.M.A. as part of the script of a proposed film: four abstained, six approved. Through the 20 years of exposure to a large variety of groups, these stages have met with no objection.

Confirmation of the truth expressed in the stages of asphyxia is found in the progressive effects of general ether anesthesia (not hypnotic, or drug relaxants), in electroshock therapy and in progressive croup in pediatrics. The effects of ether anesthesia are evident in excitement, rigidity, and relaxation; in shock therapy one sees initial depression followed by rigidity and finally relaxation. The psychiatrist is not too anxious when faced by rigidity but when relaxation appears he becomes deeply concerned. The pediatrician is willing to accept the spasticity of obstructive croup but realizes that something must be done at once when relaxation follows.

The foregoing suggests a body of truth which has been unchallenged. As such, it remains in

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the field of academic theory, unless it can be proved practical, useful, and necessary.

Methods of Treatment: The second portion of the doctrine is treatment. This emerges in three basic methods which grow out of necessity to relieve the needs of the stage of asphyxia. These three basic methods have evolved and have been employed during the last 15 years. They are nothing more than "common practice in general anesthesia" in use during the last 40 years. These methods are inhalation, transpharyngeal insufflation, and endotracheal insufflation. All mechanical devices employed for resuscitation fall into one of these three categories. Since these three methods offer the logical answer to what is to be done to relieve depression, spasticity, and flaccidity, they form the second portion of the doctrine of hypoxia.

The need for repeated reference to a definite "doctrine of hypoxia" is immediate and urgent because we must without delay state *what* we are trying to treat and *how*.

A doctrine offers a descriptive terminology enabling one to talk to another about the same thing. Common usage "asphyxiated patient" and "treatment by a resuscitator" is as vague and useless as referring to a "sick patient treated by surgery" and leaving it at that. Yet the profession drifts along, satisfied with, let us say, "mouth to mouth resuscitation for the asphyxiated patient." No one bothers to describe the degree of asphyxia in which this technic is indicated. No one seems interested in insisting that the laboratory subject, artificially relaxed by drugs, is quite different from the victim of an emergency accident, in spasticity, overcome right after he has had his dinner. Why not be realistic about the pathology faced at a given instant and let the method of treatment fit this, instead of pursuing one method at the expense of other considerations. After all, methods and apparatus are but tools to accomplish a clearly perceived objective. It does not seem to make much sense to hunt for an accident, "to try out" or "to prove" a method of treatment.

Current practice may react to the doctrine of hypoxia as too complicated. Those dealing with experimental hypoxia, on the other hand, may consider it as oversimplification. Standing between these two extremes the doctrine of hypoxia offers a practical springboard from which the physician, dentist, and the technical worker can take off to meet his specific task, secure in the knowledge that he can communicate or discuss his experience with others with similar interests, i.e., "was called to a patient, found in spasticity, who was treated at once by pharyngeal catheter inhalation, who promptly recovered into depression and then became conscious." Or, if it is explained that the patient deteriorated into flaccidity, permitting intubation without difficulty, and was carried along with endotracheal insufflation until he got rid of his carbon monoxide, he will be understood.

Even lay rescue squads are fed up with press reports that they were called to an asphyxiated patient on whom they used 1,500 gallons of oxygen without success. The inefficiency of an oxygen mask crowded over the face of a man whose airway is bubbling with vomitus or blood is perfectly apparent to any layman. It is obvious that laymen cannot teach each other but they could save many more lives if the cardiologist was alerted to the doctrine of hypoxia. The progressive effects of hypoxia having been noted and the methods of treatment alluded to, it is in order to consider these two features in detail.

The Three Stages of Asphyxia

Three stages of asphyxia are recognized, common to newborn infants as well as to adults. Since asphyxia of the newborn is a frequent occurrence, since we are present when it takes place and able to meet it without delay, it has formed a model for the treatment of all asphyxia.

(*1*) *Depression:* Although the patient appears to be unconscious with irregular breathing, and there is a tendency to duskiness, his respirations are free but slow and irregular and *he can be roused.*

(*2*) *Spasticity:* Irregular, gasping, or shallow respirations occur at intervals. There is either marked cyanosis of the mucus membranes and blotching of the skin or general pallor due to circulatory failure.

Spasm of the muscles is present, especially of the jaw, and the teeth are clenched. If suction is applied to the throat, movements of the facial muscles occur.

If the pharynx can be exposed, the pharyngeal

reflex is active; suction applied may precipitate swallowing or vomiting. Froth or fluid is likely to be present in the mouth and pharynx.

This patient is completely unconscious and cannot be roused.

(*3*) *Flaccidity:* Respirations occur at long intervals or cannot be seen. Cyanosis or pallor is present, depending on the vigor of the circulation.

There is complete relaxation of the muscles—all muscle tone is gone. Jaw is completely relaxed and there is no resistance to suction or exposure of the pharynx or larynx. Fluid is found in the hypopharynx.

The apex beat is difficult to determine.

Treatment

Treatment of *depression* is positional. The patient is to be placed on his side and covered with blankets. Oxygen inhalations may be offered. Further treatment is meddlesome.

Spasticity is important because the patient will improve to depression or deteriorate into flaccidity in accordance with the success of the treatment.

Flaccidity invites instrumentation, for the airway has become a relaxed closed cavity which can be exposed at will.

It is important to note that the stages of hypoxia are not static; they are fluid, constantly moving away from recovery or toward it. Correct treatment moves toward recovery. It is accomplished by one of three methods: inhalation, transpharyngeal insufflation, or endotracheal insufflation.

The detailed technics of treatment will be discussed in a subsequent article entitled Immediate Indoctrination.

Summary

The doctrine of the effects of hypoxia was proposed 20 years ago. It was offered to the medical profession through the specialty of obstetrics. The doctrine has been in active use since that time. The effects of hypoxia, or its physiologic pathology, carries with it the indications for treatment. These indications are to use inhalation, transpharyngeal insufflation, or endotracheal insufflation. These three methods call for three types of gadgets automatically falling into three groups. Through this classification the physician or the hospital superintendent may appraise the value of any new apparatus by determining just what it will accomplish for inhalation, transpharyngeal insufflation, or endotracheal insufflation.

Industry has accepted the value of repeated phrases for sales promotion. Will not the repetition of half a dozen medical words: depression, spasticity, and flaccidity; inhalation, transpharyngeal insufflation, and endotracheal insufflation, help clear the air and make sense out of what is treated and how, thereby saving a great many lives?

Workmen's Compensation for the Cardiac

Conference on Cardiac Disability Occurring at Work

Question of Compensability

MODERATOR: JAKUB SCHLICHTER, M.D., Assistant Professor of Medicine, Northwestern University Medical School; Associate Attending Physician, Michael Reese Hospital, *Chicago, Ill.*

PANELISTS: LOUIS H. SIGLER, M.D., Attending Cardiologist, Coney Island and Adelphi Hospitals, *Brooklyn, N. Y.*, SIMON DACK, M.D., Associate Attending Physician in Cardiology, The Mount Sinai Hospital, Assistant Clinical Professor of Medicine, New York Medical College, *New York, N. Y.*, JOSEPH D. EDWARDS, LL.B., *New York, N. Y.*, LOUIS BLOCH, LL.B., *New York, N. Y.*, JAMES BURNS, LL.B., *Pittsburgh, Pa.*

DR. SIGLER: The problem of compensability for cardiac disability occurring at work often baffles the ingenuity of the physician and attorney alike. As physicians we are, in many cases, unable to decide whether or not a cardiac attack occurring at work is causally related to the work, owing to the nature of the work, the amount of effort used in performing the work, the conflicting evidence presented by the claimant and the defendant, and the differences in authoritative opinions. Also, if causal relationship is established, the question of the duration of disability payment, its apportionment on the natural progress of the inherent underlying coronary disease or hypertension where present and other factors often have to be considered by the doctor.

We are fortunate to have with us three prominent attorneys to offer legal help in our discussion: Mr. Edwards and Mr. Bloch from New York and Mr. Burns from Pittsburgh.

The following is an illustrative case selected from my files for discussion.

CASE HISTORY

The claimant is a male, 61 years old, who worked as a cigar box maker for many years. His work consisted of picking up from time to time a bundle of wooden boards, weighing 20 to 70 lb. He would then untie the bundle, cut the boards by a machine, and construct cigar boxes with these cut boards. One day, while doing this work, he experienced sudden, severe, prolonged pain in the anterior chest with cold sweat, extreme weakness, dizziness, and collapse. He was removed to a hospital where an acute anterior myocardial infarction was diagnosed. He also showed hypertension and generalized arteriosclerosis. He remained in the hospital seven weeks and was discharged with residual electrocardiographic findings of organized infarction.

Since he left the hospital, he claimed to have experienced recurring pain in the anterior chest and interscapular region radiating to the right arm and down to the fingers on walking as little as one to one and one-half blocks. The pain also occurred, occasionally spontaneously, at times at night, lasting 10 minutes to one half hour. He also claimed to have some shortness of breath on exertion.

He filed no claim for disability compensation until about one year after the attack. The history he gave on filing his claim was that while working on the day of the attack he was compelled to do more cutting of wood than usual and that he had to carry a bundle of wood from a far corner of the room to the cutting machine. On lifting the bundle the cord broke. While making an effort to prevent the wood from falling, he developed the attack.

After he filed the claim for disability, repeated electrocardiograms were obtained. These showed the remains of the anterior left ventricular wall infarction with no

recurring active changes. After three years, however, some recurring changes in the ventricular complexes were recorded in various leads from time to time. At one time, about four years after the original attack, he showed evidence of a small area of infarction also in the posterior wall of the left ventricle.

Examination of the claimant five years after the original attack revealed a well developed individual, 66 years of age. General appearance and mentality were normal. There was some telangiectasia of the face and slight cyanotic tinge of the lips. Pupils reacted to light and accommodation. Some arcus senilis was present. Eye grounds showed 2 plus sclerosis of the retinal vessels. Heart: Apex impulse $10^1/_2$ cm to the left of the mid-sternal line in the fifth space, right border $4^1/_2$ cm from the mid-sternal line in the fourth space. Rate 78, regular sinus rhythm. First sound normal, 2nd sound normal, A_2 equaled P_2. There was a very short, localized systolic murmur at the apex. There were a few inspiratory moist rales posteriorly at the lung bases. Abdomen and extremities were negative. The peripheral palpable vessels showed slight to moderate sclerosis in various areas and no pulsation was felt over the dorsalis pedis and the posterior tibial arteries. The maximum oscillometric reading was one unit at the ankles. The blood pressure was 210/106. His vital capacity was 3,200 cc, about 75 per cent of normal.

A teleroentgenogram of the chest showed a transverse heart diameter of 15 cm with a predicted value of 13.5 cm. The aortic arch was tortuous; its transverse diameter $7^1/_2$ cm. The costaphrenic sinuses were clear and the diaphragmatic movements were free. The lungs showed some increase in the hilar and vascular markings but no parenchymal pathology. An electrocardiogram showed the remains of the old anterior wall infarction and some damage in the posterior wall of the left ventricle.

Re-examination of the patient two years later, that is, seven years after the original attack, revealed slight further increase in cardiac enlargement. The blood pressure was 235/95. The heart rate was 72 beats per minute; regular sinus rhythm was present. The lungs showed a greater increase in the hilar and vascular markings than two years previously. The vital capacity now was 2,000 cc, about 47 per cent of normal. The electrocardiogram at this time showed a marked left ventricular strain pattern and considerable changes in the ventricular complexes. All the findings indicated structural alterations in the heart that occurred since the last examination two years previously. The alterations were evidently due to progressive coronary insufficiency and his hypertensive state. Some remains of the original anterior wall infarction were still evident.

An examination of the patient one year later (more than eight years after the original attack of myocardial infarction) revealed further heart enlargement. The transverse heart diameter was about 16 cm. The heart sounds were greatly diminished in intensity. P-2 was greater than A-2. A faint systolic murmur at the aortic area was transmitted along the left sternal border. The lungs showed marked congestion at both bases posteriorly, extending to about the mid-scapular region. Expiration was considerably prolonged. The respiratory rate was 32 per minute. The liver edge extended to about 5 cm below the costal margin. There was no edema of the lower extremities. The electrocardiogram showed further alterations in the ventricular complexes in some leads.

Discussion

After going over the case in the form of a mock trial in which both the attorneys and physicians illustrated the abuses and misrepresentation that occur at Labor Department hearings, the following serious discussion of the case occurred:

Dr. Schlichter: In view of the acknowledged fact that some claimants or defendants are not entirely reliable in their claims, I would ask Mr. Bloch and Mr. Edwards to explain why the claimant filed his claim one year after the alleged accident occurred.

Mr. Bloch: I believe the claimant may have been ignorant of his rights and it was only after he realized the severity of his condition that he might have sought legal advice and was advised of his rights. Delay in filing the claim does not indicate it was an afterthought or that he has not a legitimate claim.

Mr. Edwards: I would say the fact that he filed the claim so late may indicate it was an afterthought. If he had performed his work under unusual strain on the day of his attack, he would have called it to the attention of his doctor immediately and the hospital history would indicate it.

Dr. Schlichter: I would like to know if there should be a statute of limitations in filing compensation claims.

Mr. Edwards: Yes, definitely. The purpose of a statute of limitations is to prevent the very thing that you are inquiring into now—stay of claim. Even though someone may honestly not realize he has any rights, the other party should not be asked to meet something at a very late date.

Mr. Bloch: I agree with that.

Dr. Schlichter: I would like to ask Dr. Sigler if lifting a bundle weighing 70 lb and carrying it any distance could result in a coronary occlusion, assuming that he had done the same work before.

Dr. Sigler: Yes, a person may perform

some work without any disturbance for a long time until coronary atheromatosis has reached a stage, a so-called vulnerable phase, when the same type of work, if it is severe enough, will produce an acute coronary occlusion or myocardial insult.

DR. DACK: I would be inclined to agree with what Dr. Sigler has said although it is not a simple question to answer. If the patient has evidence of coronary insufficiency, then an acute effort can produce or precipitate an attack of coronary occlusion or myocardial infarction. However, the effort would have to be strenuous, such as lifting or pulling a heavy weight.

DR. SCHLICHTER: I would like to ask Dr. Sigler to explain the mechanism of an acute cardiac insult under strain.

DR. SIGLER: We know that under strain a great number of alterations in bodily activities occur, resulting in an increase in the metabolic activity of the body, acceleration of the heart, and increase in the work of the heart. This is true especially when the person is excited during his work, causing a stimulation of the adrenals via the sympathetic system, which further increases the above factors. All these are competent producing causes of acute coronary pathologic changes in an individual who already has coronary disease. Although previously the individual had sufficient coronary supply to carry on his activities, now under the unusual strain there is an insufficient coronary blood supply, and an attack may be precipitated.

DR. SCHLICHTER: What do you think, Dr. Dack?

DR. DACK: Yes, I agree with Dr. Sigler. In fact, you don't actually have to have severe coronary sclerosis to have an acute, marked cardiac insult under unusual strain. Assuming that the history as given by the claimant is true, I think the strain was the most important factor in the onset of the acute cardiac insult which occurred in this patient.

DR. SCHLICHTER: Dr. Sigler, is there such a condition as "spontaneous" mycardial infarction or ischemia and ischemic necrosis? If so, what is the mechanism?

DR. SIGLER: The term "spontaneous" as related to an acute cardiac insult is very often a misnomer. We don't know what the term means in the pathogenesis of acute manifestations of coronary disease. I personally don't believe there is any kind of a "spontaneous" process occurring in the body. There are always some active changes going on in the body which help precipitate an acute attack of coronary disease. For instance, we know of cases where an individual will develop an acute coronary insult after a heavy meal. An individual may develop coronary insufficiency after an exciting game or after an exciting event of any kind. I feel that a coronary attack occurring in bed or while sleeping is caused by some bodily changes affecting the circulation, such as slowing of the circulation while relaxed or while asleep, resulting in coronary thrombosis. Lowering of the blood pressure and local slowing of the circulation in a diseased coronary would produce the thrombotic process.

DR. DACK: The crucial question in deciding whether a specific event caused a heart attack in any particular case is whether a "spontaneous" coronary occlusion or myocardial infarction had already begun. In other words, it is difficult for me to visualize a man with stable heart and circulation developing a myocardial infarction while lifting this table, unless certain processes had already started and progressed steadily during the previous hours or previous days. Now I feel that in practically all cases where effort is a factor in causing the attack, the acute process has probably started several hours or days before.

DR. SCHLICHTER: Because of the shortage of time we will concentrate on the case in question. What happened to this patient? After the attack the patient developed progressive angina and chronic congestive failure, and was unable to work. The questions are: Assuming that causal relationship is established, how long is the claimant entitled to disability payment? What part is to be attributed to the pre-existing hypertension and arteriosclerosis? How much of the disability is to be apportioned to the organized infarction caused by the original attack? I would like Dr. Dack and later Dr. Sigler to comment on all three questions.

DR. DACK: From a medico-legal standpoint it is very simple. This patient received compensation and will get it for the rest of his life

if he is unable to work. No matter how many times insurance companies will bring such a case into the compensation court, nine times out of ten that patient will continue to receive compensation. That has been my experience.

Now, from a purely medical point of view, I think the answer can be "yes" and "no." Let us take the case of a vigorous man of forty who develops an acute heart attack as a result of a particular strain or trauma. We must assume that he has had an injury to a coronary artery, although the remaining part of the coronary system may be fairly normal. Trauma may precipitate pathologic changes in the wall of that vessel which would persist or progress for the remainder of the patient's life. He may be disabled for life and should get compensation. On the other hand, in a patient, such as the one presented today, who already had signs of generalized and progressive arteriosclerosis not only of his coronary arteries but also of his general vascular system, the pathologic coronary changes will continue and progress. As the history states, he had several subsequent episodes of myocardial insults. I do not believe that the subsequent cardiac insults are in any way related to the effort which caused the first attack.

My personal opinion is that in the vast majority of cases of myocardial injury resulting from strain or effort, a compensation payment should be gauged entirely on the future earning capacity of the individual. We know that after a coronary attack the patient may be perfectly normal. He can go on doing a greater or lesser amount of work which in many instances is the same kind of work he was performing before. In other words, his earning capacity or his ability to return to his natural mode of life should be the guiding point.

DR. SCHLICHTER: Yes that may be true for a year. However, I would ask Dr. Sigler what happens a year later when he has another infarction which may even involve the same artery?

DR. SIGLER: This is a very good question. I personally believe that if a person has recovered well enough to continue his work and be productive or if he is left, let us say, with only about 25 per cent of disability, then 75 per cent of normality is there, and the patient is entitled to only 25 per cent disability. If this same individual develops another attack a year or two later which is the result of the natural progress of the disease, I cannot see how you can blame the subsequent attack on the strain that brought about his original attack. I believe it is an independent process. I have had patients who, for example, have had an anterior wall infarction and have recovered and performed their work almost as efficiently as before the attack. They kept on working a year, two, or three and then developed a posterior wall infarction. We cannot say that the posterior wall infarction was caused by the original accident which produced the anterior wall infarction. We know that infarction may recur in the course of coronary disease regardless of work or no work. You cannot blame the subsequent pathologic processes that occur in the heart on the original accident.

DR. SCHLICHTER: I would ask Dr. Sigler to explain, if possible, the mechanism of angina pectoris following the recovery from acute myocardial infarction whereas before the occurrence of infarction the patient was symptom-free.

DR. SIGLER: I do not believe the organized infarction is the cause of the subsequent anginal syndrome because an infarction usually destroys the nerve endings in the heart in that area, as evidenced by the fact that some individuals with an anginal syndrome before an attack no longer have angina following the attack. However, in many cases the anginal syndrome may be traceable to the original insult in the heart, as in the case under discussion. The theoretic consideration is that there is some sort of a trigger mechanism produced by the damaged area which brings angiospastic changes in the system. Another mechanism may be that when some portion of the myocardium has been destroyed, a greater burden is thrown on the rest of the myocardium and therefore a greater strain is placed on the coronary system supplying the normal myocardium.

DR. SCHLICHTER: I would ask Dr. Dack to give his opinion if the subsequent course of this patient was due only to the progressive hypertension and coronary disease or did the original infarction contribute to it?

DR. DACK: As I said before, there is no definite proof either way, but in this particular patient there is evidence of progressive arterio-

sclerosis which appeared to be independent of the original attack which followed the strain. However, it must be remembered that one infarction will predispose to further changes. Statistics show that once a patient has sustained the first attack of infarction subsequent attacks are very common during the first year or two.

PHYSICIAN IN THE AUDIENCE: What are the psychologic aspects in this case and the possibility that psychologic trauma contributed to the subsequent attacks?

DR. DACK: I have rarely seen a patient over 60 years of age return to work who has sustained an acute attack and has been granted compensation. If he turns to work, his compensation payments stop, although these may be relatively small. I believe in that type of patient the psychologic effect of medico-legal litigation plays a great part in his subsequent disability. On the other hand, most of the patients under 50 years of age whom I have seen, usually return to some type of work unless they have had a very massive coronary attack. Frequently it is almost impossible to measure objectively the amount of disease the individual has. We have to rely entirely on the subjective complaints. Many symptoms present in these cases are mostly psychologic. They feel they cannot go back to work. They do not want to go back to work. They fear that if they do, they are going to get sicker. One must also remember there is no tangible evidence in many cases to prove they have symptoms. Many claimants, I believe, are not honest in that respect.

DR. SIGLER: I agree in that respect with Dr. Dack.

PHYSICIAN IN THE AUDIENCE: How would continued physical effort following recovery from an attack of myocardial infarction affect the longevity of the patient?

DR. DACK: If a man over the age of 60 should return to a strenuous type of work requiring lifting of heavy weights, I believe that his longevity may be affected, and the incidence of subsequent attacks will increase. However, if he has a sedentary job, I do not believe that returning to work will affect his longevity in any way. In fact, it may be beneficial.

DR. SIGLER: I believe that longevity depends primarily upon the development of a collateral circulation in these people. If an individual is so endowed by nature that a good collateral circulation develops so that the heart can withstand any strain, the outlook is very good. He usually lives a much longer life than an individual whose collateral circulation is poor or who gets one attack after another before such collaterals develop. Such patients succumb to one of the attacks.

PHYSICIAN IN THE AUDIENCE: Inasmuch as compensation for cardiac disability occurring at work is not only a medical but also a legal question, what is the law and how does the law solve the problem? Why are there so many insults and bickering at compensation hearings?

MR. EDWARDS: A very good question, doctor! We are dealing with a subject of which you saw here a mock trial, preceding the serious discussion, which seems to be a travesty. I can assure you it is repeated every day, in worse fashion than you heard today. It is a legal issue and it is a medical issue. It is both. Unfortunately, there appear medical protagonists for each side, a defendant's doctor and a plaintiff's doctor instead of an impartial doctor. Since we are here before The American College of Cardiology, and since standards of proper practice may be set, may I say that the best answer to you is an attempt on the part of your own organization to set standards which may reasonably be applied in such cases. If that is so, you will find that medicine will increase in stature.

MR. BLOCH: In discussing this particular case neither Mr. Edwards nor I tried to solve it. You doctors are the ones to decide it. But I agree with Mr. Edward's remarks that most of these problems are medical questions. All the lawyer can do is set forth the highlights of his particular client's case. Bearing in mind that the patient who comes to you has been a well man before and the incident of which he complains has rendered him helpless, that he now finds himself economically distressed and cannot carry on the burdens of responsibility to his family, you want to get an honest answer from the defendant's doctor. If the medical profession will see to it that proper justice is of greatest importance, I think you'll come up with an honest solution.

MR. BURNS: As a local attorney, I would like to say something, since I am not on either side. The law in this state (Pennsylvania) is that in the case of a man suffering from a pre-existing coronary condition who develops an acute coronary attack following an ususual occurrence at work, not doing his ordinary work but doing something out of the ordinary as is alleged in the case presented here, the referee would have to find that the strain had aggravated his pre-existing condition. As long as the result of that aggravation from the physical standpoint disabled him, he would be entitled to compensation within the limits that are established. If there is total disability he is paid for life. If there is partial disability, it only goes for a fixed period of time.

CONCLUSION

The problems besetting the determination of causal relationship and degree and duration of causally related disability in compensation cases are highlighted in this panel conference. The participants felt that it would be advantageous for both sides, the claimant and the defendant, to have a panel of physicians decide the compensability of any case. From a practical standpoint, partiality cannot be avoided if the claimant and the defendant choose their own physicians to testify. The methods of choosing a panel of impartial physicians were not discussed.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Vectorcardiography vs. Electrocardiography

Query: Has vectorcardiography any established superiority to conventional electrocardiography in the diagnosis of coronary disease?

Answer: Vectorcardiography should not be regarded as a diagnostic tool to be contrasted with electrocardiography, but rather as an adjuvant to it. Its added information is contained in the presentation of time or phase relationship of voltages of electrocardiographic leads in known spatial relationship to each other. The greater yield in respect to diagnosis in coronary disease lies, in part, in a different presentation of electrical events.

Aside from presenting evidence of anteroseptal and anterior wall infarction and diaphragmatic infarction, often with greater distinctness, there is a small percentage of cases where the vectorcardiogram may furnish the only diagnostic evidence. Although infarction of the posterolateral or posterior aspect (as opposed to diaphragmatic infarction), may be suspected from progressive increase of voltage of R waves in right-sided chest leads, definite proof of it can be demonstrated only by vectorcardiographic analysis.

In respect to the more general problem of coronary disease, we have been accustomed to look diagnostically for isolated changes of T waves. In vectorcardiograms, the angular relationship between the QRS and T is furnished. Although we have learned that spatial angles of more than 60 degrees are abnormal, in its electrocardiographic correlation it may not become evident with angles of such magnitude, and only be distinctly seen with angles of 120 degrees and more. Cases with QRS-T angles up to 160 degrees have been seen where the conventional electrocardiogram appeared to be normal.

ARTHUR GRISHMAN, M.D.
New York, New York

Surgery During Anticoagulant Therapy

Query: What procedures are taken to counteract the effects of anticoagulants in coronary patients on long term anticoagulant therapy who require elective or emergency surgery?

Answer: When elective surgery is necessary in patients on anticoagulant therapy, the drugs should be stopped. When heparin is the anticoagulant drug used, surgery can be performed when the Lee-White clotting time (or the Mayor-Connell standardized clotting time) is normal. This will almost always be within 24 hours after the last dose of heparin. When the oral anticoagulants are used, surgery can be performed when the prothrombin time is close to normal, usually within three to seven days after the last dose of the drug.

If emergency surgery is necessary in a heparinized patient, the administration of one ampule of intravenous protamine sulfate immediately neutralizes the anticoagulant activity of the heparin and surgery can be performed without delay. However, repeated doses of protamine every few hours may be required for perhaps 12 hours if the heparin had been given subcutaneously or intramuscularly. Emergency surgery in a patient on oral anticoagulants requires the use of blood transfusions during surgery together with repeated injections of vitamin K_1.

HYMAN ENGELBERG, M.D.
Beverly Hills, California

Book Reviews

Coronary Heart Disease by Milton Plotz, M.D. Hoeber, New York, 1957, pp. 353, $12.00.

In writing this book Dr. Plotz has discharged his responsibility but has not taken full advantage of an opportunity. He has succeeded in weaving his own views, based on a very considerable experience, into a good review of the clinical aspects of coronary heart disease with particular emphasis on myocardial infarction. However, he has not organized the subject matter into a unified whole with a single underlying concept. He chose as his subtitle "Angina Pectoris and Myocardial Infarction" rather than "Coronary Insufficiency: Its Causes and Effects."

The 21 chapters fall into some six sections. The first section (chapter 1) on basic principles is weak and is not a good indicator of the calibre of the work as a whole. It suffers from oversimplification to the point where it could be misleading. Section 2 (chapters 2–5) is devoted to etiologic factors and constitutes a good review. Especially praiseworthy is the author's caution where facts are few and speculation abundant, coupled with his ability to insert neat "information bits," some representing gleanings from his own experience. Section 3 on Pathology (chapter 6) is brief but in keeping with the book taken as a whole. Section 4 on Symptomatology and Diagnosis (chapters 7–14) would, in my opinion, have better continuity if chapters 10–12, on Electrocardiography and Ballistocardiography, had been appended at the end of the book. The real strength of this section lies in the presentation of "Major Myocardial Infarction," which is obviously written by a clinician with great experience. "Minor Myocardial Infarction," which is contrasted with "Major Infarction" is only mentioned incidentally. A short chapter is devoted to Angina Pectoris. In other words, the "acute incident" receives nearly all of the author's attention and there is very little mention of diagnostic problems in chronic coronary heart disease in the absence of complaints on the part of the patient. Section 5 (chapters 15–20) on Treatment and Prevention is good and the evaluation of surgical treatment very good indeed. The author is to be commended for what adds up to the energetic use of conservative measures. Section 6 (chapter 21) on the Medicological Aspects represents an excellent idea and points up the changing opinions in the relation between injury and exertion and coronary heart disease.

Anyone who is a compulsive systematist, a specialist on cardiovascular dynamics, or a stylist in rhetoric can find much to criticize in this book. On the other hand, the practicing clinician will appreciate the fact that a very knowledgeable heart specialist has taken the time from a busy life to set forth his views in an easily comprehensible manner. It is "addressed to both general practitioners and specialists" and, while both might read it with profit, the specialist will find so much with which he is familiar that prime sources may furnish a greater yield for the time invested.

ASHTON GRAYBIEL, M.D.

Received for Review

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Advances in Electrocardiography, edited by Charles E. Kossmann, Grune and Stratton, New York, 1958, pp. 280, $9.75.

Current Therapy 1958, edited by Howard F. Conn, Saunders, Philadelphia, 1958, pp. 827, $12.00.

The Psychology of Medical Practice by Marc H. Hollender, Saunders, Philadelphia, 1958, pp. 276, $6.50.

Electrocardiogram Clinics by Joseph E. F. Riseman and Eliot L. Segall, Macmillan, New York, 1958, pp. 259, $10.50.

Life Insurance and Medicine. The Prognosis and Underwriting of Disease, edited by Harry E. Ungerleider and Richard S. Gubner, Thomas, Springfield, Ill., 1958, pp. 994, $16.50.

Physical Diagnosis, ed. 14 by F. Dennette Adams, Williams and Wilkins, Baltimore, 1958, pp. 926, $12.00.

Collected Papers of the Mayo Clinic and the Mayo Foundation, Volume 49, Saunders, Philadelphia, 1958, pp. 827, $13.00.

Basic Cardiology by T. E. Gumpert, John Wright and Sons, Bristol (Williams and Wilkins, American Agents), 1958, pp. 168, $6.00.

College News

SEVENTH INTERIM MEETING

AMERICAN COLLEGE OF CARDIOLOGY

Jung Hotel, New Orleans, Louisiana

November 20 to 22, 1958

Scientific Program

First Scientific Session

Thursday, November 20, 1958, 1:00 to 5:00 P.M.

PRESENTATIONS BY NEW ORLEANS GROUP

1. Heart Failure in Infancy.
   RICHARD L. FOWLER, M.D.

2. Complex Carbohydrate Substances of the Aorta and a Speculative Appraisal of Their Relationship to Disease.
   GERALD S. BERENSON, M.D.

3. The Influence of Tropical Weather on the Heart.
   GEORGE E. BURCH, M.D.

4. Hemodynamic Alterations Caused by Successful Transaortic Valvuloplasty.
   CHARLES B. MOORE, M.D.

5. Clinical Application of the Effects of Change in Cycle Length on the Rate of Repolarization in the Ventricular Myocardium and on Conductivity in the Specialized Tissues.
   MANUEL GARDBERG, M.D.

6. Myocardial Infarction in Young Adults.
   THOMAS N. JAMES, M.D. and ROBERT W. BROWN, M.D.

Fireside Conferences

Thursday, November 20, 1958, 8:30 to 10:00 P.M.

1. Pericarditis.
   LOUIS F. BISHOP, M.D.
   Assistant Clinical Professor of Medicine, New York University Medical School, New York, N. Y.
   CRAWFORD W. ADAMS, M.D.
   Instructor in Clinical Medicine, Vanderbilt University Medical School, Nashville, Tenn.

2. Use of Enzymes in the Diagnosis of Heart Disease.
   CLARENCE M. AGRESS, M.D.
   Associate Clinical Professor of Medicine, University of California Medical School, Los Angeles, Calif.
   JOHN S. LADUE, M.D.
   Associate Clinical Professor of Medicine, Cornell University Medical College, New York, N. Y.

3. Collagen Disease and the Cardiovascular System.
   EDGAR HULL, M.D.
   Professor of Medicine, Louisiana State University School of Medicine, New Orleans.
   GEORGE R. MENEELY, M.D.
   Associate Professor of Medicine, Vanderbuilt University School of Medicine, Nashville, Tenn.

4. Vectorcardiography.
   MANUEL GARDBERG, M.D.
   Clinical Associate Professor of Medicine, Louisiana State University School of Medicine, New Orleans.
   SIMON DACK, M.D.
   Assistant Clinical Professor of Medicine, New York Medical College, New York, N. Y.

5. Indications for the Use of Angiocardiography and Cardiac Catheterization.
   CHARLES T. DOTTER, M.D.
   Professor of Radiology, University of Oregon Medical School, Portland, Oregon.
   RICHARD L. FOWLER, M.D.
   Professor of Pediatrics, Louisiana State University School of Medicine, New Orleans.

Second Scientific Session

Friday, November 21, 1958, 9:00 A.M. to Noon

Symposium on
DIAGNOSIS OF ARTERIAL DISEASE

Moderator: GEORGE E. BURCH, M.D.
Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans.

1. Pathogenesis and Natural History of Peripheral Arterial Disease.
   RUSSELL L. HOLMAN, M.D.
   Professor of Pathology, Louisiana State University School of Medicine, New Orleans.

2. Clinical Evaluation.
   RAY W. GIFFORD, JR., M.D.
   Assistant Professor of Medicine, Mayo Foundation, Rochester, Minn.

3. Evaluation of Peripheral Vascular Flow.
   GEORGE E. BURCH, M.D.
   Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans.

4. Angiographic Diagnosis.
   CHARLES T. DOTTER, M.D.
   Professor of Radiology, University of Oregon Medical School, Portland, Oregon.

5. Panel Discussion.

Third Scientific Session

Friday, November 21, 1958, 2:00 to 5:20 P.M.
Symposium on
MEDICAL TREATMENT OF ARTERIAL DISEASE

Moderator: EDGAR HULL, M.D.
Professor of Medicine, Louisiana State University School of Medicine, New Orleans.

1. Acute Peripheral Arterial Occlusion.
   STANFORD WESSLER, M.D.
   Assistant Professor of Medicine, Harvard Medical School, Boston, Mass.

2. Chronic Arterial Insufficiency.
   WILLIAM T. FOLEY, M.D.
   Assistant Clinical Professor of Medicine, Cornell University Medical College, New York, N. Y.

3. Cerebral Arterial Disease.
   CLARK H. MILLIKAN, M.D.
   Associate Professor of Neurology, Minnesota Graduate School, Mayo Clinic, Rochester, Minn.

4. Indications for Surgical Intervention.
   ALTON OSCHNER, JR., M.D.
   Vascular Surgeon, Oschner Clinic, New Orleans.

5. Panel Discussion.

Fourth Scientific Session

Saturday, November 22, 1958, 9:00 A.M. to Noon
PRESENTATION OF SCIENTIFIC PAPERS BY MEMBERS

1. Acute Benign Idiopathic or Nonspecific Pericarditis Associated with the Influenza Virus.
   CRAWFORD W. ADAMS, M.D.
   Department of Medicine, Vanderbilt University Medical School, Nashville, Tenn.

2. Auscultatory and Phonocardiographic Studies of Pure Mitral Insufficiency.
   JOSEPH K. PERLOFF, M.D.
   Department of Cardiology, Georgetown University Hospital, Washington, D. C.

3. Experimental and Clinical Dissolution of Peripheral Clots by the Fibrinolytic Agent Plasmin.
   ALVIN H. FREIMAN, M.D.
   Sloan-Kettering Division, Cornell University Medical College, New York, N. Y.

4. Other papers to be announced.

5. Cine Cardioangiography; Selective Left Ventricular Opacification in Congenital Heart Disease.
   EARL K. SHIREY, M.D.
   Department of Cardiovascular Diseases, Cleveland Clinic, Cleveland, Ohio.

Fifth Scientific Session

Saturday, November 22, 1958, 2:00 to 5:00 P.M.

Symposium on
SURGICAL TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Moderator: OSCAR CREECH, JR., M.D.
WM. HENDERSON, M.D.
Chairman and Professor of Department of Surgery, Tulane University School of Medicine, New Orleans.

1. Peripheral Arterial Insufficiency.
PAUL T. DECAMP, M.D.
Assistant Professor of Surgery, Tulane University School of Medicine, New Orleans.

2. Aorta and Large Arteries.
DENTON A. COOLEY, M.D.
Assistant Professor of Surgery, Baylor University, New Orleans.

3. Cerebral Aneurysms.
RAEBURN C. LLEWELLYN, M.D.
Assistant Professor of Surgery, Division of Neurologic Surgery, Tulane University School of Medicine, New Orleans.

4. Physiology of Arteriovenous Aneurysms.
GEORGE C. MORRIS, JR., M.D.
Director of Surgical Research Laboratories, Baylor University College of Medicine, New Orleans.

5. Congenital Abnormalities of the Major Cardiac Vessels.
W. STERLING EDWARDS, M.D.
Assistant Professor of Surgery, Medical College of Alabama, Birmingham, Ala.

6. Panel Discussion.

1959 ANNUAL MEETING

The Eighth Annual Meeting of the College will be held on May 25–29, 1959 inclusive at the Benjamin Franklin Hotel, Philadelphia. Dr. Robert P. Glover has been appointed Local Convention Chairman.

Call for Abstracts of Papers

All members of the College are requested to submit or urge their associates to submit 250 word abstracts of original scientific studies in the field of cardiovascular diseases for the Annual Meeting of the College in Philadelphia on May 25–29, 1959. These abstracts are to be mailed to the Chairman of the Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., for consideration by the Program Committee.

Eight papers will be selected for presentation by members of the College at the Annual Meeting. Abstracts must be submitted by February 15, 1959. Your cooperation is essential to our having a good meeting.